Pacific Dental Conference

Welcome to the 2025 PDC

The PDC acknowledges that the conference is situated on the unceded traditional territories of the xʷməθkʷəy̓əm (Musqueam), Sḵwx̱wú7mesh (Squamish), and səlilwətaɬ (Tsleil-Waututh) Nations.

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Pacific Dental Conference

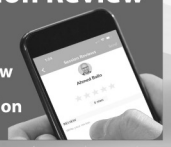
March 6-8

2025

Vancouver Convention Centre – West and East Buildings

Session Review

Please complete your review after this presentation



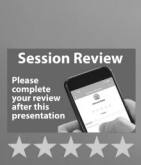
2

Pacific Dental Conference

Welcome! Let's make this session enjoyable for all. Remember to...

Session Review

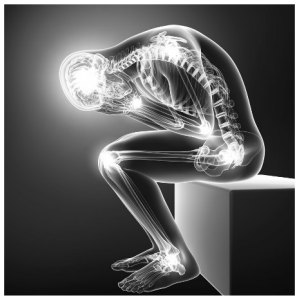
Please complete your review after this presentation



Silence Phones

3

Integrative Pain Management: A Functional Approach



Tieraona Low Dog, M.D.
Founding Director: Integrative & Functional Medicine Fellowship
Susan Samueli Integrative Health Institute
Clinical Professor, Health Sciences
University of California - Irvine

National Geographic's:
Life Is Your Best Medicine
Healthy At Home
Fortify Your Life
Guide to Medicinal Herbs

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The Epidemic of Pain

Pain affects >100 million Americans—more than heart disease, cancer, and diabetes combined.

- **~1 in 4 US adults have chronic pain.**
- Chronic pain and high-impact chronic pain (restricts life/work activities) **increase with age.**
- **Women are more likely to have chronic pain** and **high-impact chronic pain** ((25.4% and 9.6%) than men (23.2% and 7.3%, respectively)

Chronic Pain and High-impact Chronic Pain in U.S. Adults, 2023
CDC Accessed February 8, 2025

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Women in Pain

- **65% of women with chronic pain** felt physicians didn't take their **pain seriously; 45% said** they'd been labeled as **chronic complainers**.
- Women with **coronary bypass surgery are half as likely** to **be prescribed painkillers**, **compared** to **men undergoing the same procedure.**
- Women **wait an average of 65 minutes for analgesic for acute abdominal pain; men wait 49 minutes in ER in the** U.S.

https://www.health.harvard.edu/blog/women-and-pain-disparities-in-experience-and-treatment-201710091256

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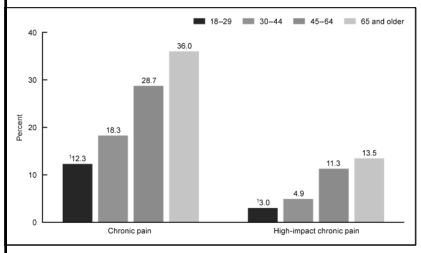
Chronic Pain



- Chronic pain is the **most common** reason adults seek **medical care.** It is the **leading cause of disability** and is associated with **decreased quality of life, isolation, and opioid misuse.**
- There is a **significant rate** of **moderate and severe mental health conditions** also associated with **chronic or persistent pain.**

Chronic Pain and High-impact Chronic Pain in U.S. Adults, 2023
CDC Accessed February 8, 2025

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The Downsides of Long-Term Opioid Use

- Opioids are effective in **short-term pain relief,** but the risks outweigh the **benefits for most people living with chronic pain.**
- For chronic *non-cancer* pain: **adverse events with opioids *78% with mid to long-term use* (average 6–16 weeks) compared to placebo.**
- **Tolerance** (need more meds for same pain relief), **increased sensitivity to pain**, **physical dependence**, **lower sex drive**, **confusion**, **constipation**, **dry mouth**, **nausea, vomiting,** increased risk of **new-onset depression after 3 months** of use.

Els C, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 2017 Oct 30;10:CD012509.

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Ibuprofen and Naproxen

- Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (**PRECISION**) trial and patient data ~ 500,000 patients: evidence "***supports avoidance of NSAID use,* if possible, in patients with, or at high risk for, cardiovascular disease.**
- If used, **shortest-duration and lowest effective dose** should be chosen, given evidence that risk is both ***duration- and dose-dependent***."
- I**buprofen** is associated with a significant increase in systolic blood pressure and a higher incidence of **newly diagnosed hypertension.**

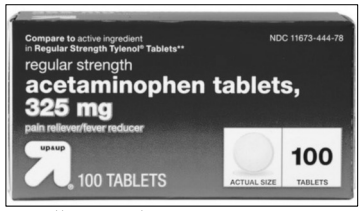
Pepine CJ, et al. *Clin Cardiol* 2017 Dec;40(12):1352-1356.
Ruschitzka F, et al. *Eur Heart J* 2017 Nov 21;38(44):3282-3292
Castelli G, et al.. *Am J Cardiovasc Drugs* 2017 Jun;17(3):243-249.

Aspirin and GI Bleeding

Garcia Rodriquez LA, et al. Bleeding Risk with Long-Term Low-Dose Aspirin: A Systematic Review of Observational Studies. *PLoS One* 2016 Aug 4;11(8):e0160046.

- Systematic review: low dose aspirin associated with **double the risk for upper GI bleeding and 80% increased risk for lower GI bleed.**
- With increased risk from low-dose aspirin (81–85 mg per day), deeply concerning about long-term use of **high-dose aspirin (2–3 g/d)** for pain.
- PPI can protect against bleed but comes with its own risks.

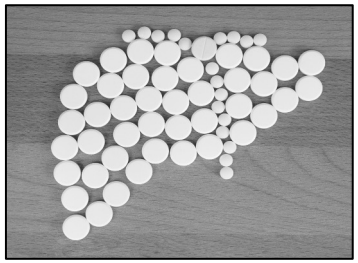
Acetaminophen (Paracetamol)



https://www.rxlist.com/tylenol-side-effects-drug-center.htm

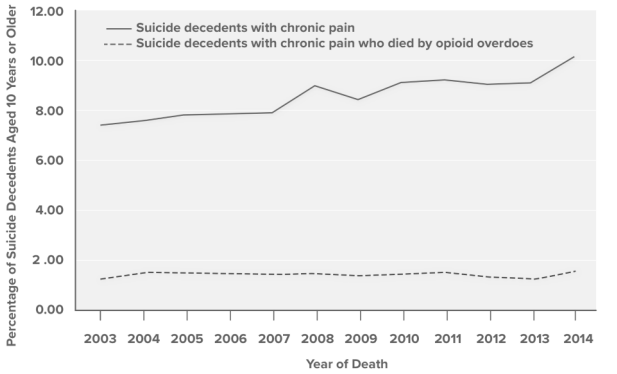
- **Approved by FDA in 1951.**
- **Superior safety** to ibuprofen, naproxen, and aspirin; commonly recommended **first-line therapy.**
- **Maximum "safe" dose is 4000 mg/d** but found in more than 600 OTC (e.g., cold, flu, fever) and prescription medications (e.g., Vicodin), *dose can add up without realizing it*.

Liver Failure



Tittarelli R, et al. Hepatotoxicity of paracetamol and related fatalities. *Eur Rev Med Pharmacol Sci* 2017 Mar;21(1 Suppl):95-101.
Weiss NS. Use of acetaminophen in relation to the occurrence of cancer: a review of epidemiologic studies. *Cancer Causes Control* 2016; 27(12): 1411–1418.

- **2017: acetaminophen is responsible** for nearly **half of acute liver failure cases i**n the US—**leading cause for liver transplantation.**
- Whether there is an increased risk of renal or blood **cancers** remains an open question.



CDC report using data from the National Violent Death Reporting System, the percentage of people who died by suicide and had evidence of chronic pain increased from 7.4% in 2003 to 10.2% 3 in 2014.

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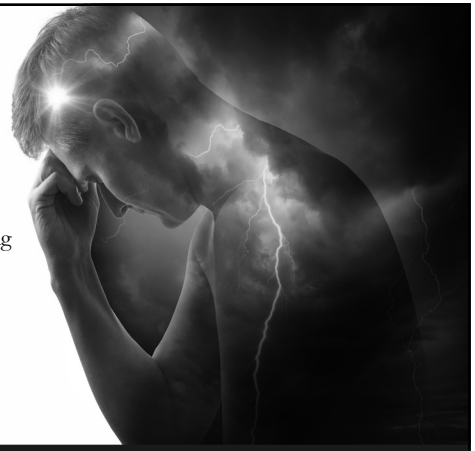
What we are doing is *not working*.
What we are doing is *dangerous*.
*De*personalized medicine is *dangerous*.

"The time has come to move past using a one-size-fits-all fifth vital sign...and reflexively prescribing an opioid when pain is characterized as severe."

Mandell BF: *Clev Clin J Med.* 2016. Jun;83(6):400-1



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Pathophysiology & Root Causes of Chronic Pain

Neuroinflammation & Central Sensitization

• Persistent activation of microglia & cytokines

Mitochondrial Dysfunction & Energy Deficits

• Chronic fatigue & pain link

Gut-Brain Axis & Pain Perception

• Dysbiosis linked to pain syndromes

Hormonal & Nutrient Deficiencies

• Cortisol dysfunction, Vitamin D, Magnesium

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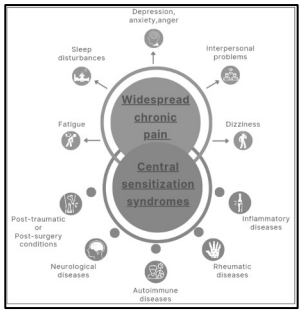
Central Sensitization

- When **CNS is repeatedly exposed to pain signals**, **neurons in the spinal cord** can become more **easily activated, amplifying pain signals.**
- People may **feel pain disproportionate** to the severity of the **initial injury, widespread pain,** and **increased sensitivity to touch, pressure, or temperature changes.**
- **Chronic inflammation, nerve damage, tissue injury, psychological stress**, and **genetic predisposition** can all contribute to the development of **central sensitization.**



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Central Sensitization

Structural and functional changes in the thalamus, hypothalamus, and amygdala

Hyperexcitability of the cell membrane of central neurons, decreased action potential threshold, increased synaptic strength, decreased descending inhibitory transmission, reduced activation threshold, and enlarged receptive fields

Loss of gray matter volume in the anterior and posterior cingulate cortex and prefrontal cortex

Heightened functional activity within the somatosensory cortex (sensory processing), insula (emotional context of sensation, sensory appraisal), and amygdala (mood processing)

Volcheck MM, et al. Central sensitization, chronic pain, and other symptoms: Better understanding, better management. *Cleve Clin J Med.* 2023 Apr 3;90(4):245-254.

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Central Sensitization

Increased temporal summation (leading to increasing ascending sensory amplification) and reduced conditioned pain modulation (reduction in descending inhibitory signals)

Maladaptive central and peripheral neuroplasticity

Hypothalamic-pituitary-adrenal axis changes

Hyperactive sympathetic nervous system and endogenous opioid system

Changes in neurotransmitter concentrations in the cerebrospinal fluid

Volcheck MM, et al. Central sensitization, chronic pain, and other symptoms: Better understanding, better management. *Cleve Clin J Med.* 2023 Apr 3;90(4):245-254.

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CENTRAL SENSITIZATION INVENTORY: PART A

Name: _____ Date: _____

Please circle the best response to the right of each statement.

1	I feel tired and unrefreshed when I wake from sleeping.	Never	Rarely	Sometimes	Often	Always
2	My muscles feel stiff and achy.	Never	Rarely	Sometimes	Often	Always
3	I have anxiety attacks.	Never	Rarely	Sometimes	Often	Always
4	I grind or clench my teeth.	Never	Rarely	Sometimes	Often	Always
5	I have problems with diarrhea and/or constipation.	Never	Rarely	Sometimes	Often	Always
6	I need help in performing my daily activities.	Never	Rarely	Sometimes	Often	Always
7	I am sensitive to bright lights.	Never	Rarely	Sometimes	Often	Always
8	I get tired very easily when I am physically active.	Never	Rarely	Sometimes	Often	Always
9	I feel pain all over my body.	Never	Rarely	Sometimes	Often	Always
10	I have headaches.	Never	Rarely	Sometimes	Often	Always
11	I feel discomfort in my bladder and/or burning when I urinate.	Never	Rarely	Sometimes	Often	Always
12	I do not sleep well.	Never	Rarely	Sometimes	Often	Always
13	I have difficulty concentrating.	Never	Rarely	Sometimes	Often	Always
14	I have skin problems such as dryness, itchiness, or rashes.	Never	Rarely	Sometimes	Often	Always
15	Stress makes my physical symptoms get worse.	Never	Rarely	Sometimes	Often	Always
16	I feel sad or depressed.	Never	Rarely	Sometimes	Often	Always
17	I have low energy.	Never	Rarely	Sometimes	Often	Always
18	I have muscle tension in my neck and shoulders.	Never	Rarely	Sometimes	Often	Always
19	I have pain in my jaw.	Never	Rarely	Sometimes	Often	Always
20	Certain smells, such as perfumes, make me feel dizzy and nauseated.	Never	Rarely	Sometimes	Often	Always
21	I have to urinate frequently.	Never	Rarely	Sometimes	Often	Always
22	My legs feel uncomfortable and restless when I am trying to go to sleep at night.	Never	Rarely	Sometimes	Often	Always
23	I have difficulty remembering things.	Never	Rarely	Sometimes	Often	Always
24	I suffered trauma as a child.	Never	Rarely	Sometimes	Often	Always
25	I have pain in my pelvic area.	Never	Rarely	Sometimes	Often	Always
					Total=	

CENTRAL SENSITIZATION INVENTORY: PART B

Name: _____

Date: _____

Have you been diagnosed by a doctor with any of the following disorders?

Please check the box to the right for each diagnosis and write the year of the diagnosis.

		NO	YES	Year Diagnosed
1	Restless Leg Syndrome			
2	Chronic Fatigue Syndrome			
3	Fibromyalgia			
4	Temporomandibular Joint Disorder (TMJ)			
5	Migraine or tension headaches			
6	Irritable Bowel Syndrome			
7	Multiple Chemical Sensitivities			
8	Neck Injury (including whiplash)			
9	Anxiety or Panic Attacks			
10	Depression			

Central Sensitization Inventory excellent test–retest reliability and internal consistency, Part A is scored from 0-4. Subclinical: 0 to 29. Mild: 30 to 39. Moderate: 40 to 49. Severe: 50 to 59.

https://www.pridedallas.com/wp-content/uploads/2016/04/csi_english.pdf
Accessed January 7, 2025

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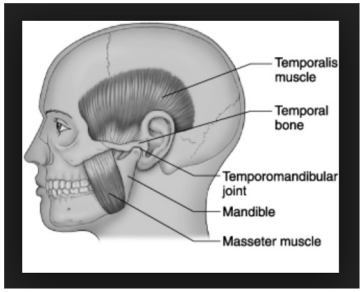
TMD Prevalence

- **Temporomandibular disorders** (TMD) are a group of **musculoskeletal diseases affecting masticatory muscles** and **temporomandibular joints** (TMJ).
- **Systematic review and meta-analysis** (n= 2518): prevalence of TMD affects up to 25% of people with a predominance **of myofascial pain diagnosis (10.3–15.4%). Women 2 x more likely to have TMD.**



Bueno CH, et al. Gender differences in temporomandibular disorders in adult populational studies: A systematic review and meta-analysis. *J Oral Rehabil.* 2018 Sep;45(9):720-729.

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Myogenous TMD and Central Sensitization

Myogenous TMD often present **overlapping features** with disorders characterized by chronic primary pain related to dysfunction of the central nervous system (CNS), **may be due to central sensitization.**

Headache, migraine, and neck pain are not only highly associated with **chronic pain-related TMD** but also **increase the risk** of their development.

Ferrillo M, et al, Pain Management and Rehabilitation for Central Sensitization in Temporomandibular Disorders: A Comprehensive Review. *Int J Mol Sci.* 2022 Oct 12;23(20):12164

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Temporomandibular pain disorder screening instrument.

1. In the last 30 days, on average, how long did any pain in your jaw or temple area on either side last?
   a. No pain
   b. From very brief to more than a week, but it does stop
   c. Continuous
2. In the last 30 days, have you had pain or stiffness in your jaw on awakening?
   a. No
   b. Yes
3. In the last 30 days, did the following activities change any pain (that is, make it better or make it worse) in your jaw or temple area on either side?
   A. Chewing hard or tough food
      a. No
      b. Yes
   B. Opening your mouth or moving your jaw forward or to the side
      a. No
      b. Yes
   C. Jaw habits such as holding teeth together, clenching, grinding or chewing gum
      a. No
      b. Yes
   D. Other jaw activities such as talking, kissing or yawning
      a. No
      b. Yes

Items 1 through 3A constitute the short version of the screening instrument, and items 1 through 3D constitute the long version. An a response receives 0 points, a b response 1 point and a c response 2 points.

TMP Pain Screening Tool

- Responses from screener can be used as **part of the process for a pain-related TMD diagnosis.**
- **Sensitivity 99.1%** for both short (3 questions) and long questionnaire (6 questions): **specificity was 95–98%.**
- **Radiographic imaging confirms TMD diagnosis.**
- Patients **are *interested in treatment.***

Gonzalez YM, et al. Development of a brief and effective temporomandibular disorder pain screening questionnaire. *J Am Dent Assoc.* 2011 Oct; 142(10): 1183–1191.

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Low Dose Naltrexone

- A **competitive opioid receptor antagonist** FDA approved to treat **both opioid and alcohol use disorders.**
- **Low-dose naltrexone (LDN) at 1-5 mg/**night (vs. 50-100 mg/d normal dose) shows promise in **reducing symptoms** related to chronic pain conditions such as **fibromyalgia, neuropathic pain, inflammatory bowel conditions, and multiple sclerosis.** it offers an option for managing **TMD with a centralized pain component**
- LDN **modulates neuro-inflammation**, perhaps due to the rebound increase in opioid receptors and anti-inflammatory properties related to LDN's toll-like receptor 4 (TLR4) antagonism.

Kim PS, Fishman MA. Low-Dose Naltrexone for Chronic Pain: Update and Systemic Review. *Curr Pain Headache Rep.* 2020 Aug 26;24(10):64.

McKenzie-Brown AM, et al. Low-Dose Naltrexone (LDN) for Chronic Pain at a Single Institution: A Case Series. *J Pain Res.* 2023 Jun 14;16:1993-1998.

Hatfield E, Phillips K, Swidan S, Ashman L. Use of low-dose naltrexone in the management of chronic pain conditions: A systematic review. *J Am Dent Assoc.* 2020 Dec;151(12):891-902.e1.

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Table 1: Evidence for Use of LDN in Pain Medicine.

Author	Study Type	Year Published	Indication	Key Finding
Smith et al[13]	Pilot study	2007	Crohn's disease	4.5 mg for 12 weeks, improved quality of life, effective in controlling symptoms of Crohn's disease
Gironi et al[14]	Phase II pilot trial	2008	Multiple sclerosis	Minor adverse effects, improvement in spasticity
Cree et al[15]	Randomized placebo cross over trial	2010	Multiple sclerosis	4.5mg for 8 weeks, improved mental health quality of life indices and symptomatic pain
Sharafaddinzade et al[16]	Randomized placebo cross over trial	2010	Multiple sclerosis	No significant difference in quality of life, safe option
Smith et al[17]	Randomized control trial	2011	Crohn's disease	4.5 mg for 12 weeks, improvement in clinical and inflammatory activity of disease compared to placebo
Younger et al[18]	Randomized control trial	2013	Fibromyalgia	4.5 mg, greater reduction in pain compared to placebo
Turel et al[5,19]	Retrospective review	2015	Multiple sclerosis	At 3.5 mg, 60% patients reported reduction in fatigue; 75% reported improved or stable quality of life.
Ludwig et al[20]	Retrospective review	2016	Multiple sclerosis	Safe, inexpensive treatment option
Parkitny et al[21]	Pilot trial	2017	Fibromyalgia	4.5 mg for 10 weeks, decreased plasma levels of proinflammatory cytokines, better pain control

Sirgla P, Sritapan Y, Yalamuru B. Low dose naltrexone: is it really worth the hype?. *ASRA Pain Medicine News* 2023;48. https://doi.org/10.52211/asra110123.010.

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Migraine Pathophysiology

- Originate from **abnormal brain activity**, particularly involving the **brainstem** and its **interaction with the trigeminal nerve**, a key pathway for **transmitting pain signals.**
- Emerging research indicates **mitochondrial dysfunction** may play a **critical role in migraine pathogenesis**. It may contribute to the **hyperexcitability of neurons,** a hallmark of migraine attacks.
- Nutrients such **as riboflavin, coenzyme Q10, and magnesium**, which **support mitochondrial function**, are often used in preventive treatment.
- **Corticol spreading depression** is a wave of **intense neuronal activity** followed by a period of neuronal silence that spreads across the cortex. It is particularly associated with the **aura phase of migraines.**

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Migraine Pathophysiology

- **Serotonin: Low** serotonin may lead to v**asodilation and the release of pro-inflammatory neuropeptides. Triptans**, which are serotonin receptor agonists, **help reduce migraine symptoms by constricting blood vessels and inhibiting neuropeptide release.**
- **Calcitonin Gene-Related Peptide (CGRP): CGRP is a potent vasodilator and is heavily involved in the pain pathways of migraines.** During a migraine, CGRP is released from the **trigeminal nerve, promoting inflammation, vasodilation, and pain transmission.** CGRP inhibitors (e.g, Rimegepant (Nurtec), atogepant (Qulipta) are new class of migraine therapies.

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Migraine Triggers

- Hormonal changes (before menstruation)
- Stress
- Anxiety
- Depression
- Lack of sleep
- Poor posture
- Strenuous exercise
- Dehydration
- Missed or delayed meals
- Weather changes (sunshine, high heat, change barometric pressure)
- Diet (varies per individual; diary is advisable

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Migraine Prophylaxis

- Talk to your HCP about **hormone options, triptans, and newer CGRP meds for migraine prevention and treatment**.
- **Limit triggers** (e.g., stay hydrated, manage sleep/stress, etc.)
- **Magnesium:** 300-600 mg/d
  - Note: **magnesium L-threonate** has better brain penetration (144 mg from 2000 mg magnesium L-threonate (*Magtein®)*
- **Riboflavin:** 400 mg/d for a minimum of 90 days.
- **CoQ10:** 200 mg/d for a minimum of 90 days.
- **Feverfew:** 500-1000 mg/d freeze-dried herb

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Magnesium

- **Low magnesium** associated with **T2DM, metabolic syndrome, inflammation, HTN, atherosclerosis, sudden cardiac death, pain, osteoporosis, migraine, asthma, and colon cancer.**
- **50% of U.S. population** consumes less than the required amount of daily magnesium.
- **Magnesium required for the activation of vitamin D.**
- FDA requires warning that **proton pump inhibitors can cause dangerously low magnesium levels.**

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Magnesium in Migraines

- Magnesium is a natural **N-methyl-D-aspartate (NMDA) receptor antagonist**, helping to prevent excessive neuronal excitation.
  - This is important because **glutamate**, an excitatory neurotransmitter, is often elevated during migraines, contributing to neuronal hyperactivity.
- It blocks **calcium channels**, which reduces calcium influx into neurons. Excessive calcium can trigger **cortical spreading depression** (CSD) thought to underlie migraine auras.
- Decreases levels of **pro-inflammatory mediators**, such as **substance P** and **calcitonin gene-related peptide (CGRP)**, implicated in migraine pain

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Magnesium for Migraine Prophylaxis

- Many migraineurs have ***decreased magnesium levels***.
- Data show Mg is more beneficial in those who have **migraine with aura** and **premenstrual migraine.**
- The American Headache Society and the American Academy of Neurology gave magnesium a Level B rating (probably effective). **They recommend it be considered for migraine preventive therapy.**

https://www.aan.com/globals/axon/assets/9774.pdf
Accessed October 4, 2024

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Migraines in Pregnancy

- Magnesium is "safe and effective preventive therapy for episodic migraines in **pregnancy**."
- Decreases the **frequency, severity, and duration of migraine headaches.**
- When additional treatment was needed, **94%** of migraines were controlled with the combination **magnesium and riboflavin**.

Assessing the efficacy of magnesium oxide and riboflavin as preventative treatment of migraines in pregnancy. *American Journal of Obstetrics Gynecology* :https://doi.org/10.1016/j.ajog.2021.11.1136.

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Magnesium and Inflammation

- Adults consuming < RDA of magnesium **1.48–1.75 times more likely to have elevated CRP** than those with normal magnesium intake.
- **Oral magnesium** supplementation **decreases CRP** levels in healthy elders, those who are obese, and those with prediabetes.
- **Hypomagnesemia may accentuate pain** by unblocking the **NMDA receptor (involved in central sensitization. Magnesium creates a blockade of the NMDA receptor in the spinal cord.**
- **Meta-analysis 20 studies**: alleviates **acute postoperative pain** and enhances effect of opioids without increase in side effects.

Shmagel A, et al. Low magnesium intake is associated with increased knee pain in subjects with radiographic knee osteoarthritis: data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2018 May;26(5):651-658; deOliveira GS, et al. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology* 2013 Jul;119(1):178-90.

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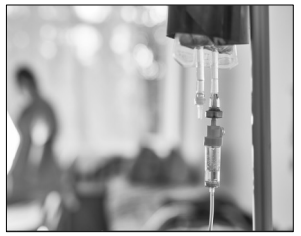
Magnesium in Other Pain Conditions

- Evidence for **magnesium in analgesic adjuvants against acute and chronic pain has accumulated over decades.**
- A potential benefit for:
  - **Perioperative administration reduces acute postop pain and analgesic use.**
  - **Peripheral neuropathy**
  - **Fibromyalgia**
  - **Dysmenorrhea**
  - **Tension headaches**
  - **TMD**



Léger M, et al. Opioid-free Anesthesia Protocol on the Early Quality of Recovery after Major Surgery (OFA Trial): A Randomized Clinical Trial. *Anesthesiology*. 2024 Apr 1;140(4):679-689.

Shin HJ, Na HS, Do SH. Magnesium and Pain. Nutrients. 2020 Jul 23;12(8):2184.

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Magnesium Supplementation

- **Magnesium L threonate** – better penetration across blood brain barrier. Studies demonstrate benefits in sleep[1], augmentation of opioids in cancer pain[2], and possibly ADHD.[3]
- **Magnesium citrate, malate, and glycinate** are equal choices for supplementation.
- Dose is 300-600 mg for migraines.

1. Hausenblas HA, et al. Magnesium-L-threonate improves sleep quality and daytime functioning in adults with self-reported sleep problems: A randomized controlled trial. Sleep Medicine X 2024; Volume 8: 100121
2. Wu S, et al. Oral application of magnesium-L-threonate enhances analgesia and reduces the dosage of opioids needed in advanced cancer patients-A randomized, double-blind, placebo-controlled trial. *Cancer Med.* 2023 Feb;12(4):4343-4351.
3. Surman C, Yasudreuil C, Boland H, Rhodewalt L, DiSalvo M, Biederman J. L-Threonic Acid Magnesium Salt Supplementation in ADHD: An Open-Label Pilot Study. *J Diet Suppl.* 2021;18(2):119-131

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Riboflavin for Migraines

- Plays a crucial role in **mitochondrial energy production. Migraines have been associated with mitochondrial dysfunction,**
- **Canadian Headache Society** guidelines gave **strong recommendation** for benefit, and minimal side effects.
- **AAN/AHS give riboflavin Level B recommendation, probably effective** and should be considered for migraine prevention. Adults: 400 mg/d Children 100-200 mg/d
- *Deficiency: increases* ***light sensitivity.***

Rajapakse T, et al. Nutraceuticals in migraine: a summary of existing guidelines for use. *Headache* 2016; Apr;56(4):808-16.

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Supplement Facts
Serving Size: 2 Caplets • Servings per bottle: 30

Amount Per Serving		%Daily Value
Riboflavin (Vitamin B-2)	400mg	30,769%
Magnesium (Citrate and Oxide)	360mg	86%
Proprietary Complex*** Puracol® Feverfew (whole leaf and extract)	100mg	**

** Daily Value Not Established
*** Puracol® is a proprietary complex of whole leaf feverfew containing a broad spectrum of naturally occurring phytochemicals and a unique feverfew extract.

Supplement facts
Serving Size: 3 Veg Capsules
Servings Per Container: 60

	Amount Per Serving	%Daily Value
Magnesium (elemental) (from 2,000 mg Magtein® Magnesium L-Threonate)	144 mg	34%
Magtein® (Magnesium L-Threonate)	2 g (2,000 mg)	†

†Daily Value not established.

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Coenzyme Q10 and Mitochrondria

- A **lipid-soluble antioxidant** and a crucial component of the **mitochondrial electron transport chain** (ETC).
- **Mitochondrial dysfunction** implicated in the pathophysiology of various pain conditions, including **fibromyalgia, neuropathic pain, migraine, and muscle pain.**
- When mitochondrial function is impaired, **ATP production decreases, and oxidative stress increases, contributing to cellular damage and inflammation.**
- CoQ10 reduces oxidative stress within the mitochondria, **diminishing inflammation and the sensitization of pain pathways.**

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Coenzyme Q10 in Pain

- **Fibromyalgia**: 15 studies, most **had improvements in pain, fatigue, sleep, tender points, mood disorders**, and Fibromyalgia Impact Questionnaire (FIQ) scores.
- **Migraine**: Meta-analysis of RCTs, supplementation significantly **reduced the frequency and severity of migraines.**
- **Statin-Induced Myopathy**: Statin drugs can impair mitochondrial function, leading to muscle pain. Supplementation shown to **reduce the severity of muscle pain in some individuals taking statins** (Tomaszewski et al., 2021).
- **Neuropathic Pain**: Growing body of evidence suggests CoQ10 is an effective **adjunctive** therapy in **neuropathic pain, including trigeminal neuralgia.**
- **Dose is generally 200-300 mg/d** as ubiquinol (or ubiquinone)

Freire de Carvalho J, Skare T. Coenzyme Q10 supplementation in rheumatic diseases: A systematic review. *Clin Nutr ESPEN*. 2024 Feb;59:63-69.
Sazali S, et al. Coenzyme Q10 supplementation for prophylaxis in adult patients with migraine: a meta-analysis. *BMJ Open*. 2021 Jun 5;11(1):e039358.
Qu H, et al, Effects of Coenzyme Q10 on Statin-Induced Myopathy: An Updated Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc*. 2018 Oct 2;7(19):e009835.
Khuankaew C, Apaijai N, Sawaddiruk P, et al, Effect of coenzyme Q10 on mitochondrial respiratory proteins in trigeminal neuralgia. *Free Radic Res*. 2018 Apr;52(4):415-425.

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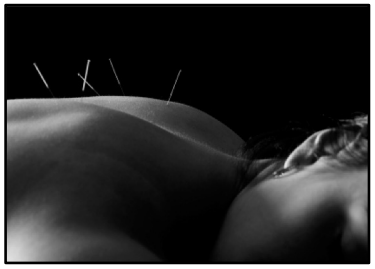
Acupuncture for Migraine

- Cochrane review 22 trials (n=4985): evidence suggests adding acupuncture to symptomatic treatment reduces frequency of headaches.
- Trials also suggest that ***acupuncture may be at least similarly effective as treatment with prophylactic drugs.***
- **"Acupuncture can be considered a treatment option for patients willing to undergo this treatment."**



Linde K, et al. Acupuncture for the prevention of episodic migraine. *Cochrane Database Syst Rev* 2016; Jun 28; (6):CD001218

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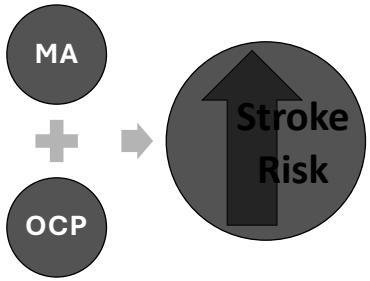
Migraine, OCPs, & Stroke



IHS: low-dose estrogen in women with simple visual aura

ACOG: progestin only, intrauterine or barrier contraception

WHO: absolute contraindication in all women with aura

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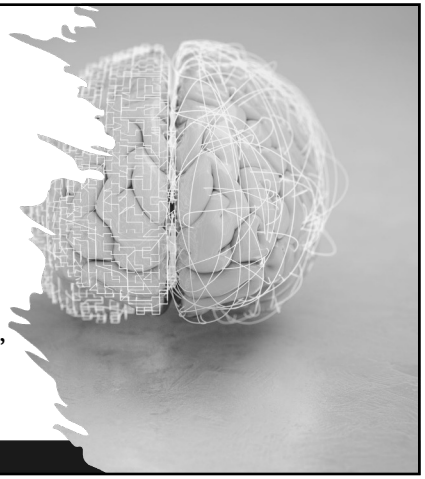
The MGBA Axis

- Growing recognition **gut microbiota** plays a crucial role in **regulating emotions, behavior, higher cognitive functions, and even pain** through **the 'microbiome-gut-brain axis (MGBA).'**
- Researchers found loss of **intestinal barrier regulation** and **microbiota diversity** and subsequent **increase in systemic inflammation** can have far-reaching effects on **cardiovascular, metabolic, neurological, and psychiatric health**.[1]



1. Camilleri M, et al. *Gut* 2019; 68:1516–1526

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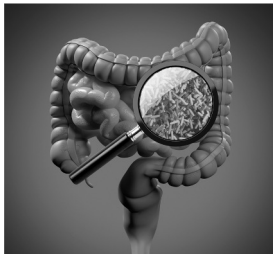
Dysbiosis

- Dysbiosis: an ***imbalance*** **in bacterial composition**, changes in bacterial **metabolic activities**, and/or changes in **bacterial distribution** within the gut.[1]
- Dysbiosis is associated with **autoimmune disease, obesity, cardiovascular, metabolic, mental health disorders, infection, pain, certain cancers**, and **oral health**.



1. DeGruttola AK, Low D, Mizoguchi A, Mizoguchi E. Current Understanding of Dysbiosis in Disease in Human and Animal Models. *Inflamm Bowel Dis.* 2016 May;22(5):1137-50.

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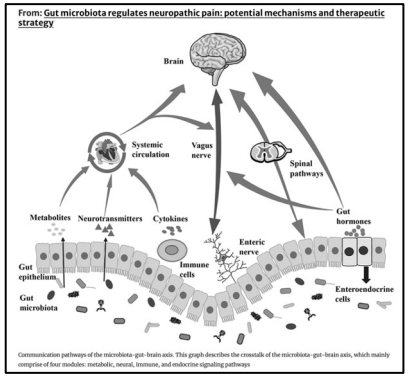
- Gut **dysbiosis** is associated with the **progress** of different **chronic pain** disorders, such as **visceral pain, neuropathic pain, inflammatory pain, migraine, and fibromyalgia.**
- Different **signaling molecules** (e.g., metabolites, neuromodulators, cytokines, neurotransmitters) from the gut microbiota regulate the **progression of chronic pain by modulating peripheral and central sensitization.**



Liu L, et al. Gut microbiota in chronic pain: Novel insights into mechanisms and promising therapeutic strategies. *Int Immunopharmacol.* 2023 Feb;115:109685.

Image: Lin B, et al. *J Headache Pain.* 2020 Aug 17;21(1):103.

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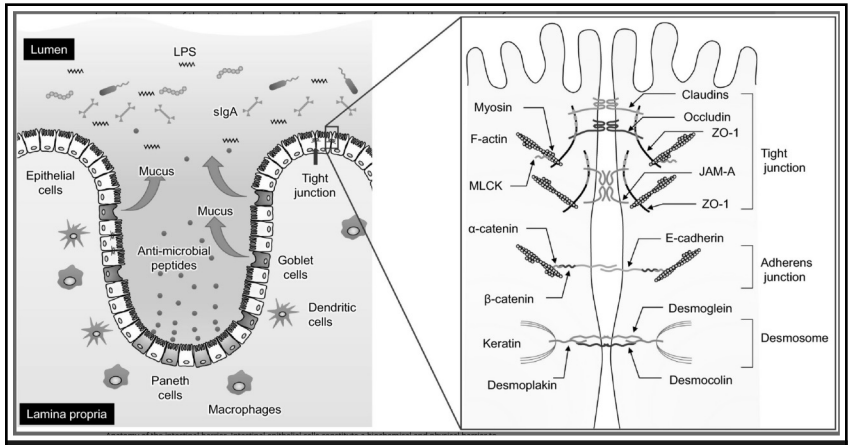
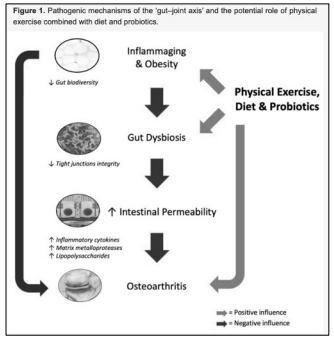
Intestinal Permeability & Inflammation

- **Selective ability** allows water, electrolytes, and digested food to be absorbed, **while keeping harmful substances out** of the bloodstream.
- Disruption of **tight junctions** increases **intestinal permeability**, allowing larger molecules, bacteria, and endotoxins to pass through lining.
- **Endotoxins** are lipopolysaccharides (**LPS**) abundant in **gram-negative bacterial membranes** (70% of gut bacteria). Highly immunogenic, LPS binds TLR-4, triggering immune cells to **release inflammatory cytokines, driving systemic inflammation.**

Boutagy NE, et al. *Biochimie* 2016; 124: 11–20



Dysbiosis, Leaky Gut, LPS, and Osteoarthritis

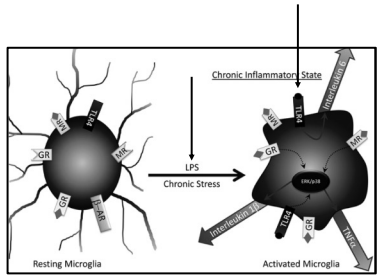


- **Trauma, lifestyle** (e.g., diet, obesity, and metabolic disease), and **frequent antibiotic use** can disrupt the human microbiome and promote the **leakage of bacterial endotoxins and metabolites, such as LPS, into circulation.**
- **Increased levels of LPS** are associated with **knee osteophyte severity and joint pain.**

Rahman SO, et al. The Potential Role of Probiotics in the Management of Osteoarthritis Pain: Current Status and Future Prospects. *Curr Rheumatol Rep.* 2023 Dec;25(12):307-326.

LPS and Neuro-inflammation

- **LPS enter circulation**, are highly immunogenic, **bind TLR-4**, trigger **systemic inflammation**, and degrade **BOTH intestinal** and **blood-*brain* barriers.**
- **TLR-4** on microglia and neurons: **once activated,** produce **pro-inflammatory cytokines (TNF-α, IL-1β, NO).**
- LPS induces **cognitive impairment, anxiety, depression** in animal models.



Zhao J, et al. *Sci Rep* 2019; 9:5790 doi:10.1038/s41598-019-42286-8
Kure C, et al. *Front Pharmacol* 2017; doi.org/10.3389/fphar.2017.00117

Aspect	Key Points	Mechanism of Action	Clinical Evidence	Interventions & Dosing
Gut Microbiota	Dysbiosis is linked to increased pain perception	Alters neurotransmitter production (e.g., GABA, serotonin)	Dysbiosis present in IBS, fibromyalgia, chronic pain (Zhou et al., 2020)	Probiotics (*Bifidobacterium longum 1714*, 10-20 billion CFU/day)
Gut Permeability	"Leaky gut" contributes to systemic inflammation	Allows LPS and pro-inflammatory molecules into circulation	Associated with neuroinflammation in chronic pain (Kelly et al., 2021)	*L-glutamine* (5 grams 1-2x/day), *Zinc carnosine* (75 mg/day)
Neuroinflammation	Chronic activation of microglia enhances central sensitization	Microbial metabolites (e.g., SCFAs) reduce microglial activation	*Butyrate* supplementation reduced pain in neuropathic models (Bajic et al., 2020)	*Butyrate* (500-1000 mg/day), *Curcumin* (500-1000 mg/day)

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Aspect	Key Points	Mechanism of Action	Clinical Evidence	Interventions & Dosing
Vagus Nerve	Critical in gut-brain communication	Transmits anti-inflammatory signals from gut to brain	*Lactobacillus rhamnosus GG* enhances GABA receptor expression (Bravo et al., 2011)	Probiotics (*Lactobacillus rhamnosus GG*, 10-20 billion CFU/day)
Neurotransmitter Production	Gut bacteria produce GABA, serotonin, dopamine	Influences mood, pain perception, and stress response	Prebiotics increased serotonin precursors, reducing anxiety and pain (Schmidt et al., 2015)	*Prebiotics* (e.g., GOS, FOS) 5-10 grams/day
Dietary Influence	Diet modulates microbiota composition and inflammation	Anti-inflammatory diets support gut-brain axis	Mediterranean and low FODMAP diets reduce pain in IBS and chronic pain (Guida et al., 2020)	*Low FODMAP Diet*, *Mediterranean Diet*, *Specific Carbohydrate Diet*

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Lab Test	Test Name	Lab Company	Test Description
Comprehensive Stool Analysis (CSA)	• Comprehensive Stool Analysis • Comprehensive Stool Analysis • Comprehensive Stool Analysis	• Mosaic Diagnostics • Access Med Lavs • Doctor's Data	Evaluates digestive efficiency, enzyme levels, microbial diversity, and presence of pathogens. Tracks inflammation markers and screens for bacteria, parasites, and yeast.
Fecal Calprotectin	• Calprotectin • Calprotectin Stool	• Diagnostics Solutions • Doctor's Data	Measure calprotectin levels to detect intestinal inflammation. Helps diagnose conditions like IBD and monitor disease activity.
SIBO Breath Test	• SIBO/IMO Pediatric Lactulose Breath Test • SIBO Breath Test - Glucose • trio-smart SIBO Breath Test • SIBO- 3 Hour	• Commonwealth Diagnostics International • Aerodiagnostics LLC • Gemelli Biotech • Genova Diagnostics	Diagnoses SIBO by measuring hydrogen and methane gases produced by bacteria in the small intestine. Requires fasting and carbohydrate substrate ingestion.
Zonulin Test	• Zonulin Add-On • Zonulin Family Protein Add-On • Add-On: Zonulin	• Diagnostic Solutions • Doctor's Data • Genova Diagnostics	Measures zonulin protein levels to assess intestinal permeability, potentially indicating a compromised intestinal barrier.
GI Pathogen Panel/ Profile	• GI Pathogens Profile • GI Pathogens Profile multiplex PCR • GI Effects® Gut Pathogen Profile	• Diagnostic Solutions • Doctor's Data • Genova Diagnostics	Screens for bacterial, viral, and parasitic infections contributing to gastrointestinal symptoms.

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Diet: A Modifiable Lifestyle Factor

- Chronic pain is **a pro-inflammatory** state that drives **peripheral and central sensitization.**
- Preliminary evidence suggests **daily fruits, vegetables, olive oil, nuts, and legumes** (i.e., **Mediterranean**-style diet) with **omega-3, vitamin B12, and magnesium,** and **reduced processed foods** are anti-inflammatory in chronic pain and can minimize analgesic use.
- Intermittent fasting also shows promise for all pain types.

Philpot U, et al. Diet therapy in the management of chronic pain: better diet less pain? *Pain Management* 2019; 9(4); doi.org/10.2217/pmt-2019-0014

52

Review: 172 Studies to Reduce Inflammation

Rondanelli M, et al. Food pyramid for subjects with chronic pain: foods and dietary constituents as anti-inflammatory and antioxidant agents. *Nutr Res Rev.* 2018 Jun;31(1):131-151.

- **Diet** optimal for **reducing *pro-inflammatory states* associated with chronic pain.**
- Daily: **low GL diet with minimum of 5 servings of fruits and vegetables.**
- Weekly: **4 portions legumes/fish, two portions white meat, two portions cheese, and one portion red meat.**
- **Only occasional sweets.**

Vienna Low Dog, M.D.

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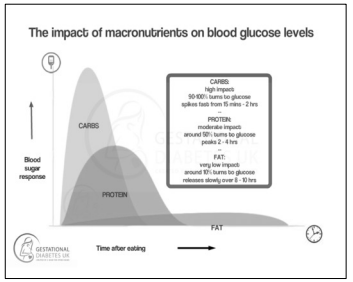
Low Glycemic Load Diet

- Overdo refined carbs, **blood sugar rises, insulin released, store** extra glucose as **fat, drive inflammation.**
- Blood sugar goes up and then can plummet, **leaving one tired and disrupting sleep/wake cycle.**
- High sugar diets cause **dysbiosis and degrade intestinal barrier, leading to systemic inflammation.**
- **Low glycemic load diet lowers CRP (inflammation) p<0.05)[1]**



1. Chiavaroli L, et al. *BMJ.* 2021 Aug 4;374:n1651.

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Dietary Fiber and Gut Microbiome

- **Gut microbiome** critical intermediary between **diet and inflammatory disorders**, metabolic syndrome, obesity, and behavioral dysregulation.
- **High fiber diets** reduce incidence/mortality of many chronic diseases.
- **Low soluble fiber diets** *reduce gut microbial diversity,* particularly those that produce SCFA, and **increase intestinal permeability.**
- Systematic review: **higher dietary fiber intake associated with lower risk of respiratory infection and lower odds of depression.**
- Need **25-34 g/d** of fiber (6-10g soluble).

Ma, W., *et. al.* Dietary fiber intake, the gut microbiome, and chronic systemic inflammation in a cohort of adult men. *Genome Med* 2021; 13: 102 doi.org/10.1186/s13073-021-00921

Fatahi S, et al. Association of dietary fiber and depression symptom: A systematic review and meta-analysis of observational studies, Comp Ther Med 2021; 56: 102621

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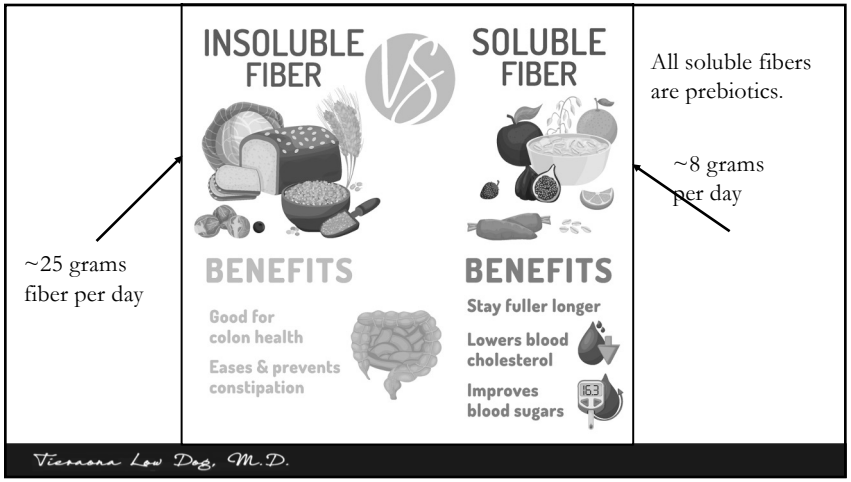

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Fresh & Dried Fruits	Serving	Soluble Fiber (g)	Insoluble Fiber (g)	Total Fiber (g)
Apple with skin	1 medium	4.2	1.5	5.7
Apricots, dried	4 medium	1.8	1.7	3.5
Banana	1 medium	2.1	0.7	2.8
Blackberries	½ cup	3.1	0.7	3.8
Figs, dried	3 medium	3.0	2.3	5.3
Grapefruit	½ of large	2.4	0.7	3.1
Kiwi	1 large	2.4	0.8	3.2
Orange	1 medium	2.1	1.3	3.4
Pear	1 medium	0.8	3.2	4.0
Plums	2 medium	1.2	1.0	2.2
Prunes	4 medium	1.3	1.8	3.1
Raspberries	½ cup	0.9	2.3	3.2
Strawberries	1 cup	1.8	2.6	4.4
Nuts, Seeds & Beans				
Almonds, raw	1 ounce	0.7	3.5	4.2
Black beans, cooked	½ cup	3.8	3.1	6.9
Flaxseeds	2 tbsp.	2.7	2.1	4.8
Garbanzo beans, cooked	½ cup	1.2	2.8	4.0
Kidney beans, cooked	½ cup	2.9	2.9	5.8
Lentils, cooked	½ cup	2.8	3.8	6.6
Peanuts, dry roasted	1 ounce	1.1	1.2	2.3
Pinto beans, cooked	½ cup	5.5	1.9	7.4
Psyllium seeds	2 tbsp.	7.1	0.9	8.0
Sesame seeds	¼ cup	0.7	2.6	3.3
Split peas, cooked	½ cup	1.1	2.4	3.5
Sunflower seeds	¼ cup	1.1	1.9	3.0
Walnuts	1 ounce	0.6	2.5	3.1

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Vegetables	Serving	Soluble fiber (g)	Insoluble fiber (g)	Total fiber (g)
Artichoke, cooked	1 medium	4.7	1.8	6.5
Asparagus, cooked	½ cup	1.7	1.1	2.8
Broccoli, raw	½ cup	1.3	1.4	2.7
Brussel Sprouts, cooked	1 cup	1.7	1.9	3.6
Carrot, raw	1 medium	1.1	1.5	2.6
Green peas, cooked	½ cup	3.2	1.2	4.4
Green beans, cooked	½ cup	0.8	1.2	2.0
Kale, cooked	1 cup	2.1	5.1	7.2
Lima beans, cooked	½ cup	2.1	2.2	4.3
Potato with skin	1 medium	2.4	2.4	4.8
Soybeans (edamame)	½ cup	2.7	2.2	4.9
Squash, summer, cooked	½ cup	1.3	1.2	2.5
Sweet potato, peeled	1 medium	2.7	2.2	4.9
Tomato with skin	1 medium	0.3	1.0	1.3
Zucchini, cooked	½ cup	1.4	1.2	2.6
Whole Grains				
Barley, cooked	½ cup	3.3	0.9	4.2
Brown rice, cooked	½ cup	1.3	0.1	1.4
Oat bran, cooked	¾ cup	2.2	1.8	4.0
Oatmeal, cooked	1 cup	2.4	1.6	4.0
Popcorn, air-popped	3 cups	3.2	0.4	3.6
Pumpernickel bread	1 slice	1.5	1.2	1.7
Rye bread	1 slice	1.9	0.8	2.7
Wheat bran	½ cup	11.3	1.0	12.3
Wheat germ	3 tbsp.	3.2	0.7	3.9
Wholegrain bread	1 slice	2.8	0.1	2.9
Whole wheat bread	1 slice	1.6	0.3	1.9
Wholegrain pasta	1 cup	4.1	2.2	6.3

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Probiotics

1. **Modulating the Gut-Brain Axis**:
   - Can regulate the **HPA axis,** reducing **cortisol** (linked to **depression and pain**).
   - Gut microbes produce **neurotransmitters** (e.g., serotonin, GABA, dopamine) **that influence mood and pain.**
2. **Reducing Systemic Inflammation**:
   - **Reduce pro-inflammatory cytokines (e.g., IL-6, TNF-α)**
3. **Improving Dysbiosis**:
   - **Correcting the microbial imbalances** commonly seen in pain and depression
4. **Enhancing Short-Chain Fatty Acid (SCFA) Production**:
   - SCFAs like butyrate **strengthen the gut barrier, reduce leaky gut, and modulate brain inflammation.**

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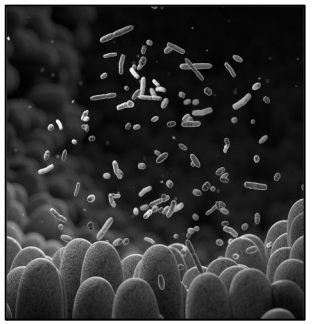
Probiotics

- Exert therapeutic effects on brain and central nervous system by **improving integrity of gut lining, reducing ability of endotoxins to leak into bloodstream and in turn, decreasing systemic inflammation.**
- Reduction of inflammation often results in **improved regulation of HPA axis and neurotransmitter activity.**



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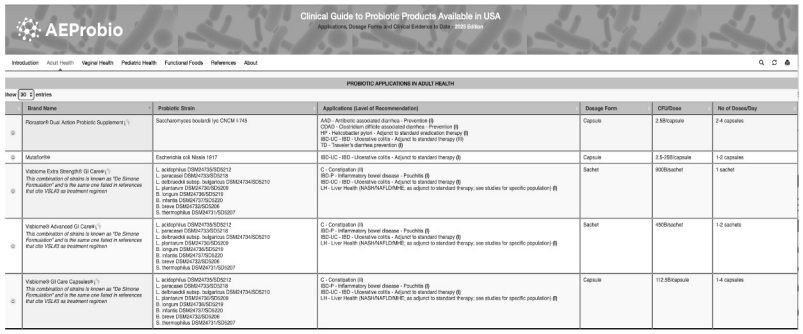

www.probioticguide.com

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Yogurt

- Subjects who ingested yogurt with ***Bifidobacterium animalis* subsp. *lactis* (BB-12)** experienced significant anti-inflammatory effect.
- Probiotics (*Lactobacillus bulgaricus*, *Streptococcus thermophilus*, *Lactobacillus acidophilus* 74-2, *Bifidobacterium animalis* subsp. *lactis* DGCC 420) also have **anti-inflammatory and immunomodulatory activity** as demonstrated by numerous intervention studies.

Live Active Cultures
S. thermophilus, L. bulgaricus, Bifidobacterium BB-12®, L. acidophilus, L. paracasei and *L. rhamnosus.*

Meng, H, et al. Consumption of *Bifidobacterium animalis* subsp. *lactis* BB-12 in yogurt reduced expression of TLR-2 on peripheral blood-derived monocytes and pro-inflammatory cytokine secretion in young adults. *Eur J Nutr* 2017; 56: 649–661.

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The Importance of Hydration

- **Adequate water intake** depends on many factors, such as **age, sex, environmental conditions, activity level and level of sweating.**
- **Hypohydration has been shown in studies to *increase baseline pain sensitivity and pain perception*, as well as fatigue.**
- Likely due to increase in blood cortisol.

Bear T, et al. A preliminary study on how hypohydration affects pain perception. *Psychophysiology.* 2016 May;53(5):605-10.
Moyen NE, et al. Hydration status affects mood state and pain sensation during ultra-endurance cycling. *J. Sports Sci.* 2015;33(18):1962-9

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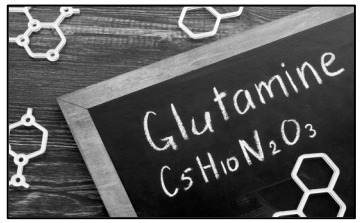
Glutamine and Intestinal Permeability

- Supports **assembly and stability of tight junction proteins, reducing the risk of increased intestinal permeability.**
- Primary energy source for supporting **renewal and repair** of intestinal epithelial cells, crucial for **integrity of intestinal barrier.**
- Involved in **synthesis of mucin, which** acts as a **physical barrier** that helps prevent attachment of pathogens and **protects lining from damage.**



Achamrah N, et al. *Curr Opin Clin Nutr Metab Care.* 2017 Jan;20(1):86-91
Wu D, et al. *Redox Biol.* 2023 Feb;59:102581.

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Supplement Facts

Serving Size 1 Teaspoon (5 g)
Servings Per Container 23

Amount Per Serving		% Daily Value
L-Glutamine (free-form)	5000 mg	*

* Daily Value not established.

Dose: 5 grams two times per day for 6-8 weeks for intestinal barrier repair.

Tieraona Low Dog, M.D.

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Zinc and Intestinal Barrier Function

- Zinc is important in maintaining tight intestinal junctions and reducing systemic inflammation.
- Zinc deficiency is linked to elevated TNF-α levels and diminished barrier integrity.
- Low zinc can increase risk of depression.
- Note: opioids deplete serum zinc.
- Dose 15-30 mg per day (do not exceed 40 mg/d long-term).

Zupo R, et al. *Nutrients.* 2022 Sep 29;14(19):4052.
Ciubotariu D, et al. *Subst Abuse Treat Prev Policy.* 2015 Aug 4;10:29.

Tieraona Low Dog, M.D.

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	VITAMIN D
Function	Promotes calcium absorption and maintains adequate serum calcium and phosphate concentrations. Involved in modulation of cell growth, neuromuscular, hormone, and immune function; and glucose metabolism. Involved in regulation of hundreds of genes.
Clinical Use	Bone pain, muscle weakness, osteomalacia, high risk for falls/fractures Prediabetes, pregnancy, chronic pain
Deficiency Signs	Musculoskeletal pain, muscle twitches, spasms, poor gait Poor immune function
Status Indicator	25(OH)D: IOM: sufficiency 20 ng/mL, severe deficiency <12 ng/mL Endocrine Society: deficiency <20 ng/mL
Typical Dosing	400 IU daily for infants less than one year, exclusively or partially breastfed 600 IU daily for those ages 1 to 70 years of age 800 IU daily for all adults up >70 years Tolerable upper limit: 4-8 years 3000 IU/d; those 9 years and older: 4000 IU/d Deficiency: 4000–5000 IU/d (100–125 µg) or 50,000 IU/wk for 2-3 months, recheck Take with vitamin K2 (100-200 mcg), ensure adequate magnesium and calcium
Forms	D_2 (ergocalciferol) – from mushrooms D_3 (cholecalciferol) – from lanolin or lichen, superior form

Tieraona Low Dog, MD

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Vitamin D

- **Hypovitaminosis D** is associated with **osteoporosis, musculoskeletal problems, chronic pain**, particularly **widespread pain.**
- Low levels of vitamin D are associated with **increased central hypersensitivity** and **severity of somatic symptoms in chronic pain** patients.
- Supplementation with vitamin D **can improve the quality of sleep, mood, and the level of pain, particularly in those with fibromyalgia and musculoskeletal pain.**

Thomas CM, et al. Vitamin D supplementation for pain. *US Pharm* 2015; 40: 43–46.
McCabe PS, et al. Low vitamin D and the risk of developing chronic widespread pain: results from the European male ageing study. *BMC Musculoskelet Disord* 2016; 17, 32
Shipton, EE & Shipton, EA Vitamin D deficiency and pain: clinical evidence of low levels of vitamin D and supplementation in chronic pain states. *Pain Ther* 2015; 4, 67–87.

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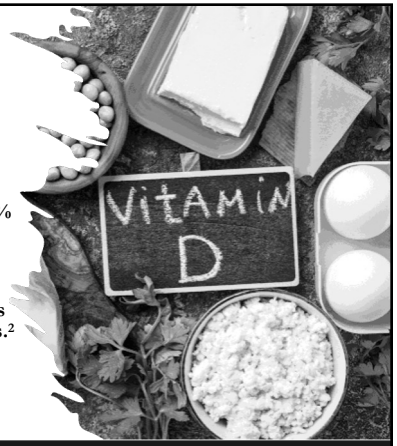
Statins, Vitamin D, and Myopathy

- **Meta-analysis 9 cohort studies** (n=2906): 25OHD levels in patients with **statin-related myopathy were significantly lower than patients without myopathy.**
- Subset studies: **statin tolerance** improved to **89%** ($p < 0.001$) after **D supplementation.**[1]
- **Patients should have levels corrected to sufficient levels (>30 ng/mL).**
- **Women are more likely to stop/switch statins** because of **new/worsening muscle symptoms.**[2]



1. Hou G, et al *Am J Cardiovasc Drugs* 2022 Mar;22(2):183-193.
2. Karalis DG, et al. *J Clin Lipidol.* 2016 Jul-Aug;10(4):833-841.

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Vitamin D and Pain Studies

- **Meta-analysis 19 studies**: suggest benefit for **patients with chronic pain.**
- **Meta-analysis 81 studies:** 25(OH)D levels **significantly lower** in those with **arthritis, muscle pain, and widespread chronic pain.**
- **Swedish review:** patients with **25-OHD levels <12 ng/mL** most likely to benefit from supplementation: **25-OHD >20 ng/mL less benefit.**
- I recommend blood testing for vitamin D levels and aiming for a 25(OH)D level of **40-50 ng/mL.**
- Otherwise, **2000-4000 IU per day** for otherwise healthy adults (take with **vitamin K2** – often included in multivitamins – ensure adequate Ca and Mg).

Wu Z, et al. Effect of Vitamin D Supplementation on Pain: A Systematic Review and Meta-analysis. *Pain Physician* Sep-Oct 2016;19(7):415-27.
Wu Z, et al. The association between vitamin D concentration and pain: a systematic review and meta-analysis *Public Health Nutr* 2018 Aug;21(11):2022-2037;
Helde-Frankling M, et al. Vitamin D in Pain Management. *Int J Mol Sci* 2017 Oct 18;18(10):2170.

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Vitamin D Levels

25(OH)D Concentration	Vitamin D Status
<20 ng/mL (<50 nmol/L)	Vitamin D deficiency
20–30 ng/mL (50–75 nmol/L)	Vitamin D insufficiency
→ 30–50 ng/mL (75–125 nmol/L)	Vitamin D sufficiency
50–60 ng/mL (125–150 nmol/L)	Safe but not a target concentration
60–100 ng/mL (150–250 nmol/L)	Area of uncertainty with potential benefits or risks
>100 ng/mL (>250 nmol/L)	Potential vitamin D toxicity (oversupply)

Pludowski P, et al. Clinical Practice in the Prevention, Diagnosis and Treatment of Vitamin D Deficiency: A Central and Eastern European Expert Consensus Statement. *Nutrients.* 2022;14:1483. doi: 10.3390/nu14071483.

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OMEGA 3 FATTY ACIDS

BRAIN, HEART, AND PAIN

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PRESS RELEASE

The Fatty Acid that May Help Reduce Chronic Pain

Elucidating the molecular targets of 'eicosapentaenoic acid': A natural remedy for chronic pain

by Okayama University

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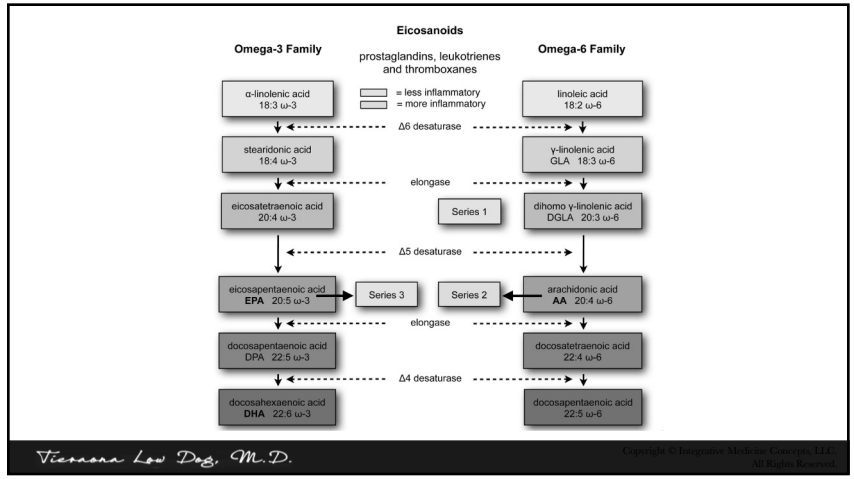

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Omega 3 and Pain

- Systematic review/meta-analysis: **omega-3 fatty acid supplementation moderately improves chronic pain**.
- **Increasing omega-3 intake** reduced patient-reported **joint pain** and **morning stiffness** in patients **with rheumatoid arthritis** or **joint pain secondary to inflammatory bowel disease.**

Philpot U, et al. Diet therapy in the management of chronic pain: better diet less pain? *Pain Management* 2019

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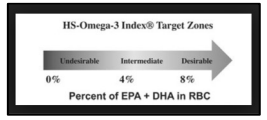
Omega 3 Index Status

- The **US (excluding Alaska), Canada, Germany, and Italy** have seen improvement and are now in the **"low category."**
- **Spain** has moved from the low to the **"moderate"** category.
- **South Korea, Japan, and Alaska's average Ω-3i were >8%.**
- **Total fish and shellfish intake:**
  - US 4.38 kg/capita/y
  - Germany 14.1 kg/capita/y
  - Japan (45.5 kg/capita/y)
  - South Korea 55.0 kg/capita/y



Schuchardt JP, et al. Red blood cell fatty acid patterns from 7 countries: Focus on the Omega-3 index. *Prostaglandins Leukot Essent Fatty Acids.* 2022 Apr;179:102418.

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Omega 3 Index and Outcomes

- Observational and cross-sectional studies showed that **lower Ω-3i is associated with increased risk for ischemic stroke, heart disease, chronic pain, reduced brain volume, impaired cognition, progression to dementia, postpartum depression, and psychiatric diseases.**
- Ω-3i >8% can be achieved by eating fish, taking omega-3 supplements, and consuming omega-3 fortified foods.
- It takes **1 gram/d fish oil** to raise Ω-3i levels.
- It should be **2:1 EPA-DHA.**
- Microalgal forms are also effective.

Schuchardt JP, et al. Red blood cell fatty acid patterns from 7 countries: Focus on the Omega-3 index. *Prostaglandins Leukot Essent Fatty Acids.* 2022 Apr;179:102418.

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Mood, Sleep, and Pain

- Study 273,952 individuals/47 countries found **depression significantly associated with severe pain** (odds ratio 3.93).
- High prevalence of **concomitant pain and sleep disturbance.**
- **Short sleep duration increases risk for developing chronic pain.**
- Study healthy young women found after just **two nights of fragmented sleep**: increased pain sensitivity in both superficial and deep tissues.

McWilliams LA, et al. A *Clin J Pain* 2017 Oct;33(10):899-904.
Iacovides S, et al. *J Pain* 2017 Jul;18(7):844-854.

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Restorative Sleep

- A study of **172,321 adults** found that **men with adequate sleep live ~5 years longer than men without; women live ~2 years longer.**
- **Prolonged lack of restorative sleep increases belly fat, raises blood pressure, accelerates aging of the heart, increases perception of pain, and prevents flushing of toxins from the brain, increasing the risk of cognitive decline.**
- **Note: Rule out RLS, sleep apnea, etc.**

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Sleep Foundation Best Apps 2025

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Evidence-Based Supplements

- **Melatonin**[1]
- Dose: 1-5 mg, 60 minutes before bedtime.
- Circadian rhythm disorders, jet lag, and to support sleep onset.
- **L-Theanine**[2]
- Dose: 200-400 mg, 30-60 minutes before bedtime.
- Reduces stress and anxiety, improves sleep quality
- **Magnesium L-threonate**[4]
- Dose: 120-150 mg elemental mag (2 g mag L-threonate); 30-60 minutes before bed.
- It promotes relaxation and improves sleep quality.

1. Fatemeh G, et al. *J Neurol.* 2022 Jan;269(1):205-216. 2. Moshfeghinia R, et al. *BMC Psychiatry.* 2024 Dec 4;24(1):886
3. Bulman M, et al. *Proceedings* 2023, *91*(1), 32; https://doi.org/10.3390/proceedings2023091032. 4. Hausenblas HA, et al. *Sleep Med X.* 2024 Aug 17;8:100121

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The End

There is **so much more to say**!
But that is all for today.

Thank you!

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