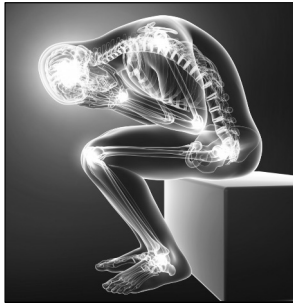


An Integrative Approach to Pain



Tieraona Low Dog, MD

Chair: US Pharmacopeia Dietary Supplement Admissions,
Evaluation & Labeling Expert Committee

Clinical Associate Professor of Medicine
University of Arizona (Retired)

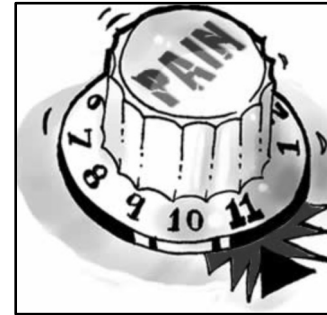
National Geographic's:
Life Is Your Best Medicine
Healthy At Home
Fortify Your Life
Guide to Medicinal Herbs
www.DrLowDog.com

Disclosure: Neither I nor members of my immediate family have any financial relationships with commercial entities that may be relevant to this presentation.

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1

The Epidemic of Pain



- **>100 million Americans**—more than heart disease, cancer, diabetes combined.
- 50 million adults have **chronic pain**.
- 20 million report **severe pain**.
- **1 in 5 Canadians live with chronic pain; 1:3 over the age of 65. Consumes 10% of all health care costs.**
- Incidence:
 - chronic low back pain (29%)
 - arthritis pain (28%)
 - neck pain (15%)
 - migraine headache (13%)
 - TMD (11%) in adults.

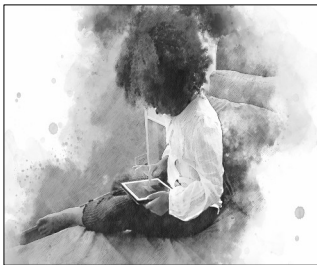
<https://www.cdc.gov/mmwr/volumes/67/wr/mm6736a2.htm>

Accessed March 1, 2022

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2

Pain in Children



- Prevalence of **chronic pain increases with age in children/teens** with female preponderance.
- Median prevalence of idiopathic pain (e.g., **headache, functional abdominal pain, back pain, musculoskeletal pain**) 11–38% in community surveys.
- High prevalence rates of **pain due to disease**.
- Up to **38% of youth suffer from chronic pain**; large number of adolescents prescribed opioids for headaches and sports injuries.
- More than **one in four opioid overdoses** involve children/adolescents.

Lioessi C, et al. Pediatric Chronic Pain: Biopsychosocial Assessment and Formulation *Pediatrics* November 2016, 138 (5) e20160331
Crit Care Med 2020. doi: 10.1097/01.ccm.0000618708.38414.ea

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Classification based on origin



Neuropathic pain
pain arising from nervous system

Radicular pain
pain arising from spinal cord

Nociceptive pain
pain arising from tissue damage

Visceral pain
(internal pain)

Somatic pain
(External pain)

Classification based on duration

Chronic pain
long lasting pain

Acute pain
short intense pain

4

Chronic and Acute Pain

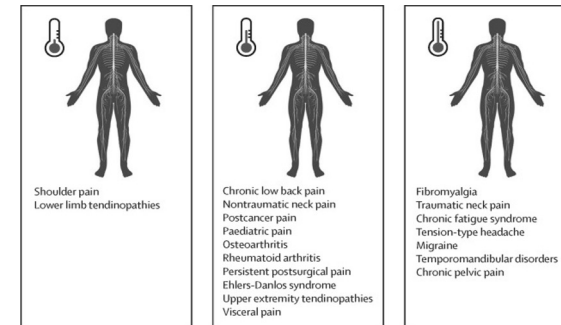
- Pain is **not an input** - pain is an **output from the brain**.
- Thermal, chemical or mechanical message** is sent to spinal cord, transferred to **different parts of the brain (neuromatrix)** to interpret and respond.
- When noxious stimulus present for **more than 12 weeks**, changes occur in peripheral and central nervous system: **increased receptor field size**, **reduced threshold** for activation and enhanced activation of neuromatrix; **amplifying pain**.
- This is known as **central and/or peripheral sensitization of pain**.
 - Allodynia** (something *which isn't painful feels painful*)
 - Wind up** (when *repeated stimulus* becomes pain)
 - Hypersensitivity** (*increased* pain levels for painful stimulus)

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Degrees of Central and Peripheral Sensitization



The Lancet Rheumatology 2021 3:e383-e392DOI: (10.1016/S2665-9913(21)00033-1)
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Opiates

- Opioid industry > \$13 billion-a-year. Americans **comprise ~4% of the world's population, use > 30% of all opioids**. US accounts for ~100% of hydrocodone (*e.g.*, Vicodin), 81% for oxycodone (*e.g.*, Percocet).
- Clinicians ill-prepared to deal with complex problems associated with chronic pain - **creates easy atmosphere for prescribing pain meds**.
- Pharmaceutical companies pumped millions of dollars into telling physicians and public that medications were **safe and effective for chronic pain**.
- Opioids effective for **short-term pain relief** but **risks often outweigh benefits for many people living with chronic pain**.

Haffajee RI, et al. Drug Companies' Liability for the Opioid Epidemic *N Engl J Med* 2017; 377:2301-2305
<https://nich.nih.gov/drug-topics/opioids/opioid-overdose-crisis>. Accessed April 25, 2022

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The Downside to Long-Term Use

- For chronic *non-cancer* pain: **adverse events with opioids 78% with mid to long term use (average 6–16 weeks) compared to placebo**.
- Opioid medications commonly reduce motility, delay transit and gastric emptying, and suppress androgen and adrenal function
- Tolerance** (need more medication for same pain relief), **increased sensitivity to pain, physical dependence, lower sex drive, confusion, constipation, dry mouth, nausea, and vomiting**, and an 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 & 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*.”
- **Ibuprofen** associated with **significant increase in systolic blood pressure** and 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.

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Non-Steroidal Anti-Inflammatories



- Increase **gut permeability, inflammation, and risk of gastrointestinal injury** (e.g., ulcers).
- **FDA warning about NSAID use in patients with cardiovascular disease released in 2005 and strengthened in 2015**, yet data show those **with CVD are more than twice as likely to use NSAIDs than those without CVD**.

Castelli G, et al. Rates of Nonsteroidal Anti-Inflammatory Drug Use in Patients with Established Cardiovascular Disease: A Retrospective, Cross-Sectional Study from NHANES 2009-2010. *Am J Cardiovasc Drugs* 2017 Jun;17(3):243-249.

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Aspirin & GI Bleeding



Garcia Rodriguez 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 own risks.**

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Acetaminophen and Liver Toxicity



- **Superior safety** to ibuprofen, naproxen, and aspirin; commonly recommended **first line therapy**
- Over past 40 years, **acetaminophen (paracetamol) toxicity** accounts for **46% of all acute liver failure in the US and 40–70% of all cases in Great Britain and Europe**.
- 1975 *Lancet* editorial, “Surely it is time to replace paracetamol with an effective analogue which cannot cause liver damage.”

Tittarelli R, et al. Hepatotoxicity of paracetamol and related fatalities. *Eur Rev Med Pharmacol Sci* 2017 Mar;21(1 Suppl):95-101.

Lee WM. Acetaminophen toxicity: a history of serendipity and unintended consequences. *Clin Liver Dis* 2020; 16(Suppl 1): 34–44.

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The Need for Alternatives



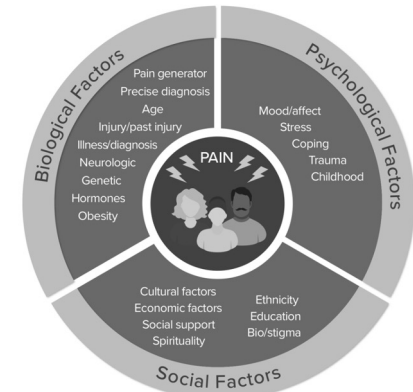
- Although advances have been made in treatments for chronic pain, it remains inadequately controlled for many people, including children.
- **Chronic pain is leading indication for complementary and integrative medicine: 33% of adults and 12% of children.**
- “A **cultural transformation** is necessary to better prevent, assess, treat, and understand pain of all types. Healthcare providers should increasingly aim at **tailoring pain care** to each person’s experience and **self-management of pain** should be promoted.”

<http://som.edu/Reports/2011/%20Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research/Report-Brief.aspx>

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- Chronic pain from **any cause** cannot be viewed as **purely physical OR psychological**, nor is a unimodal approach likely to succeed.
- Comorbid symptoms include **diminished physical functioning, sleep disturbance, fatigue, and difficulties with concentration.**
- High comorbidity with **anxiety/mood disorders.**



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Chronic Pain and Inflammation

- **Persistent low-grade systemic inflammation** associated with chronic pain
- **Chronic metabolic inflammation** often evoked by **calorie rich, nutrient depleted diets**. This dietary pattern activates neuroglial cells leading to **CNS sensitization**. It can cause **dysbiosis and intestinal permeability**, allowing the translocation of bacterial fragments (LPS), **triggering inflammation**.
- **Prolonged elevation plasma insulin levels** can **produce systemic inflammation**.
- **Excess of omega-6 fatty acids relative to omega-3 fatty acids** loads the arachidonic acid pathway and **contributes to a pro-inflammatory state**.

Zhou WBS, et al. *Front Mol Neurosci* 2021; 14: 785214.

Brain K, et al. *J Clin Med* 2021 Nov; 10(21): 5203.

Nijis J, et al. *Expert Opin. Ther. Targets*. 2020;24:793–803.

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Diet: A Modifiable Lifestyle Factor for Chronic Pain



- Evidence suggests **low glycemic load Mediterranean pattern diet: olive oil, daily fruit and vegetables, nuts and legumes, weekly 4 portions legumes/fish, 2 portions of white meat, 1 portion of red meat; with omega-3, B-vitamins and magnesium, and reduction in processed foods** is anti-inflammatory and can reduce analgesic use.
- **Intermittent fasting** shows promise for reducing pain and inflammation.

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

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; 31(1), 131–151

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| Inflammatory Food Ratings | | FOOD | SERVING SIZE | SERVING SIZE (GRAMS) | IF RATING |
|---------------------------|------------------------------|----------------------|--------------|----------------------|-----------|
| 200 or higher | Strongly anti-inflammatory | AGAVE NECTAR | 1 TBSP | 21 | -74 |
| 101 to 200 | Moderately anti-inflammatory | ALMOND BUTTER | ¼ CUP | 64 | 100 |
| 0 to 100 | Mildly anti-inflammatory | CHEESE, CHEDDAR | 1 OUNCE | 28.35 | -20 |
| -1 to -100 | Mildly inflammatory | CHICKEN BREAST, RSTD | 3 OUNCES | 85 | -19 |
| -101 to 200 | Moderately inflammatory | MILK, WHOLE | 1 CUP | 246 | -46 |
| -201 or lower | Strongly inflammatory | OLIVE OIL | 1 TBSP | 14 | 74 |
| | | ONIONS, COOKED | ½ CUP | 105 | 240 |
| | | RICE, WHITE | 1 CUP | 158 | -153 |
| | | SPINACH | 1 CUP | 30 | 75 |
| | | SALMON, SOHO BAKED | 3 OUNCES | 85 | 450 |
| | | TURMERIC | ½ TSP | 1.5 | 338 |

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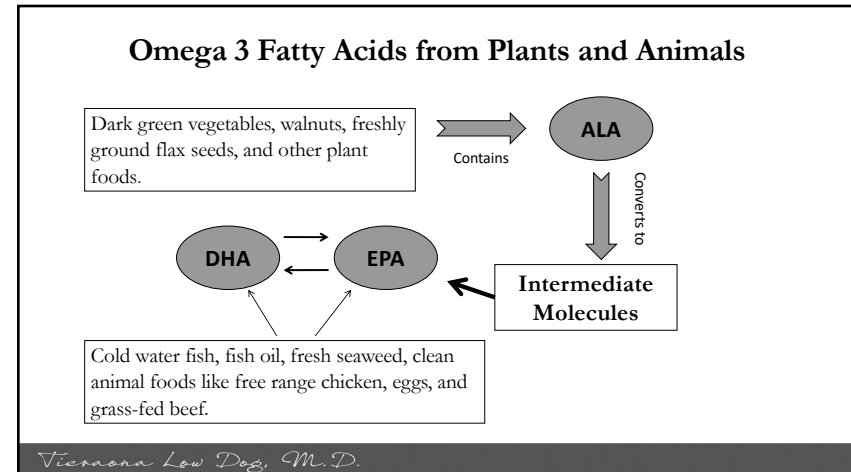
Existing User? [Login](#)

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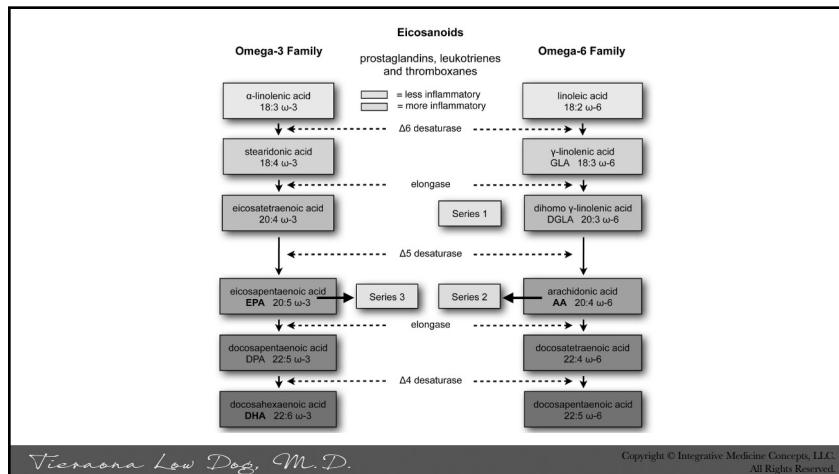
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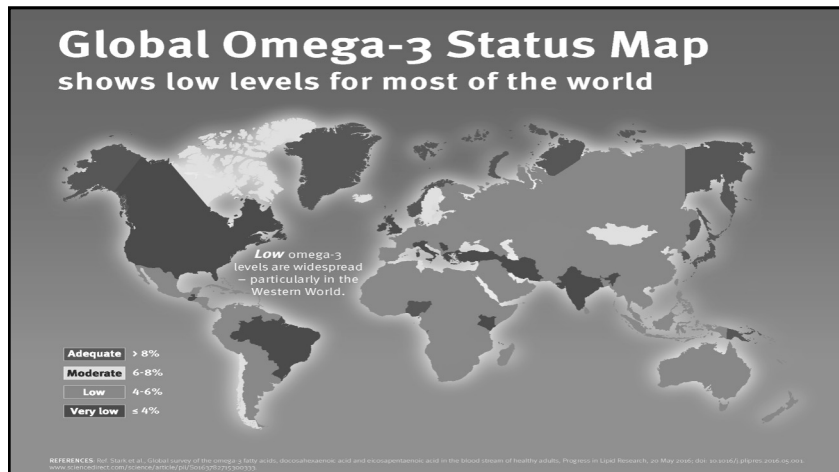
Omega-3 Fatty Acids

- Preclinical findings: dietary omega-3/omega-6 ratio appears to be significant in inflammatory 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

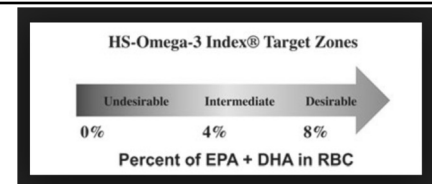
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Omega-3 Index



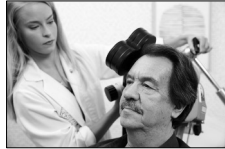
- Omega-3 Index indicates % of EPA+DHA in red blood cell fatty acids.
- What about chronic pain patients? Should we assess omega-3 fatty acid level to optimize their “anti-inflammatory” activity?
- Consider 2 g/day omega-3 (~1,000–1,200 mg EPA; 400–800 mg DHA).
- FDA has set 3 grams of omega-3 per day as a safe level.

Langlois K, et al. *Health Rep* 2015; Nov 18;26(11):3-11

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Transcranial Magnetic Stimulation



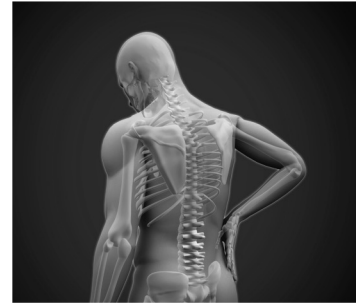
- TMS applies **gentle magnetic pulses** (like magnetic field in MRI machine) to targeted areas of brain, enhancing “**neuroplasticity**,” helping restore normal function.
- Evidence based guidelines:
 - **Level A evidence** (definite efficacy) for neuropathic pain, depression, motor recovery post-stroke. (FDA approved depression and OCD)
 - **Level B evidence** (probable efficacy) for fibromyalgia, Parkinson's disease, lower limb spasticity in MS, PTSD, chronic post-stroke aphasia.
- Treatments generally 10-45 minutes 5 days/week for 6 weeks. More than half patients report significant improvement within just a few treatments.
- Contraindicated: seizure disorders and metal in head/neck.

Lefaucheur JP, et al. *Clin Neurophysiol* 2020 Feb;131(2):474-528

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Other Options



Evidence continues to support the effectiveness of **exercise, psychological therapies, multidisciplinary rehabilitation, spinal manipulation, massage, and acupuncture for chronic low back pain.**

Chou R, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017 Apr 4;166(7):493-505.

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Topical Analgesia

- Menthol long history as **topical analgesic**. TRPM8 channels are “menthol receptors.”
- Clinical studies report topical **menthol** as **safe and effective in treating variety of painful conditions**: musculoskeletal pain, sports injuries, neuropathic pain and migraine.

Pergolizzi JV, et al. The role and mechanism of action of menthol in topical analgesic products. *Journal of Clinical Pharmacy and Therapeutics* 2018; 43(3): 313-319

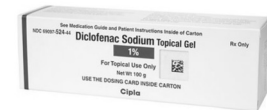


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Topical NSAIDs



- **Cochrane review 39 studies** (10,631 patients) found that **gel preparations of diclofenac and ketoprofen** provide good pain relief over placebo for patients with **osteoarthritis**.
- Oral administration **NOT** superior to topical.

Adili A, et al. Cochrane in CORR: Topical NSAIDs for chronic musculoskeletal pain in adults. *Clinical Orthopaedics and Related Research* 2018; 476(11): 2128-341

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Alpha Lipoic Acid

- **α -lipoic acid (ALA, thioctic acid)** naturally occurring compound produced by humans (and others).
- Potent **antioxidant and anti-inflammatory**, resides in mitochondria. It **increases glutathione** and can **scavenge heavy metals** in animal studies and **improves insulin signaling**.
- Johns Hopkins review: multiple studies show **ALA can improve pain of diabetic peripheral neuropathy (moderate strength of evidence)**.

Nesbit SA, et al. Non-pharmacologic treatments for symptoms of diabetic peripheral neuropathy: a systematic review. *Curr Med Res Opin* 2019 Jan;35(1):15-25.

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Diabetic Peripheral Neuropathy

- **200 people with diabetic peripheral neuropathy:** randomly assigned to **add on oral 600 mg ALA twice daily** (n=100) or placebo (n=100) for **6 months**.
- Those taking ALA had significantly better results in **vibration perception threshold, neurological symptom score, neurological disability score, and visual analog scale**. Adverse events similar to placebo.
- “Oral 600 mg ALA twice daily treatment for DPN over 6 months is effective, safe, and tolerable.”

El-Nahas MR, et al. Oral Alpha Lipoic Acid Treatment for Symptomatic Diabetic Peripheral Neuropathy: A Randomized Double-Blinded Placebo-Controlled Study *Endocr Metab Immune Disord Drug Targets*. 2020 May 5.

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ALA Take Home Notes

- **R enantiomer** superior to S enantiomer. **Liquid** superior to solid.
- Dose is **600 mg 2 times daily** on an **empty stomach**.
- Preliminary data suggests **potential benefit for burning mouth syndrome, PCOS, endometriosis, multiple sclerosis, traumatic brain injury, migraine**.
- Of note, the *IMPALA* trial *did NOT show benefit in those with fibromyalgia administering 1663 mg per day*.

DeSouza CNS, et al. Alpha-lipoic acid in the treatment of psychiatric and neurological disorders: a systematic review. *Mol Brain Dis* 2019 Feb;34(1):39-52.
Gibson I, et al. Double-blind, randomized, placebo-controlled crossover trial of alpha-lipoic acid for the treatment of fibromyalgia pain: the IMPALA trial. *Pain* 2020 Aug 5; doi: 10.1097/j.pain.0000000000002028.

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Spinal Manipulation for Acute Back Pain

- 15 RCTS found **spinal manipulation** resulted in an **improvement in pain** of about **10 points** on a **100-point scale**.
- 12 RCTS found **spinal manipulation** resulted in **improvements in function**.
- Most reported **adverse events** were musculoskeletal related, transient in nature, and of **mild to moderate severity**.



Paige NM, et al. Association of Spinal Manipulative Therapy With Clinical Benefit and Harm for Acute Low Back Pain: Systematic Review and Meta-analysis. *JAMA*. 2017;317(14):1451-1460.

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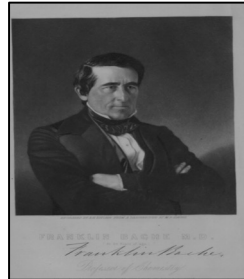
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Acupuncture in the United States

- **Dr. Franklin Baché**, great grandson Benjamin Franklin founder University of PA/first medical school in US, noted **acupuncture highly effective for pain-management**. 1825: translated **French text** on acupuncture into English.
- *Elements of Operative Surgery* (1829) contained section describing acupuncture techniques.
- 1836: **Dr. William M Lee** recommended acupuncture for pain relief in *Southern Medical Journal* and *Boston Medical and Surgical Journal* published article on **acupuncture for pain management**.
- With opiates and syringes, it fell into relative obscurity.



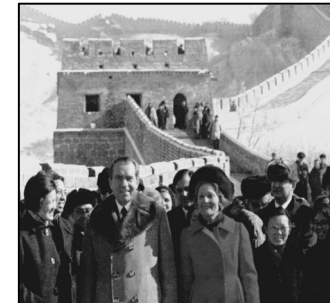
Lu DR, et al. An Historical Review and Perspective on the Impact of Acupuncture on US Medicine and Society. *Med Acupuncture* 2013 Oct; 25(5): 311-316.

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Nixon, China, and Acupuncture

- In **1972**, James Reston, *New York Times* reporter **fell ill with appendicitis** while covering President Nixon's trip to China.
- Surgeons in Beijing successfully used **acupuncture as anesthesia** during the reporter's surgery and then to **control post-operative pain**. He was *awake* whole time.
- Acupuncture part of **comprehensive system of medicine** that uses a very **different diagnostic criteria** than that used in western medicine.



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Acupuncture for Chronic Pain

Outcomes in chronic pain have been conflicting, however a meta-analysis evaluating data for 20,827 patients from 39 clinical trials found **acupuncture effective for the treatment of chronic musculoskeletal, headache, and osteoarthritis pain; treatment effects persist over time.**

Vickers AJ, et al. Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. *J Pain* 2018 May;19(5):455-474.

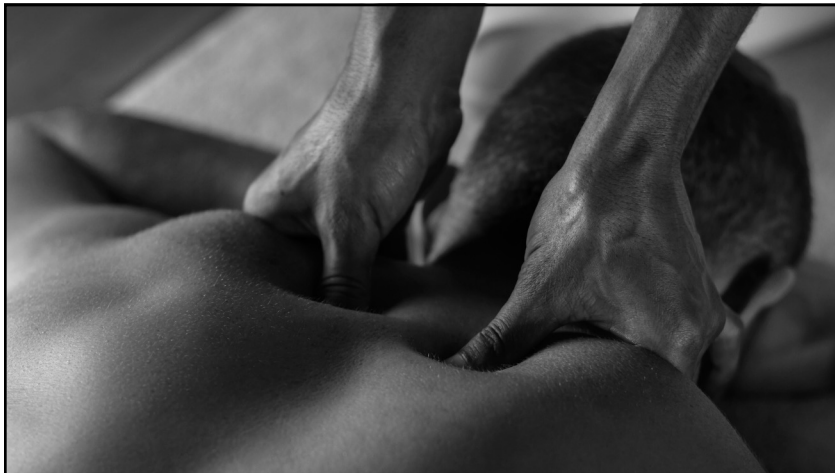


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The screenshot shows the NCCAOM (National Certification Commission for Acupuncture and Oriental Medicine) website. At the top, there are navigation links: 'FIND A PRACTITIONER', 'SEARCH', and 'LOG IN'. Below the NCCAOM logo, there are links for 'ADVOCACY / REGULATORY', 'CERTIFICATION', 'EDUCATION', 'RESOURCES', 'ABOUT', 'CONTACT', and 'LOGIN'. The main content area features a large image of wooden drawers with metal knobs. Below the image, the text reads 'NCCAOM® Find a practitioner Directory' and 'www.nccaom.org'.

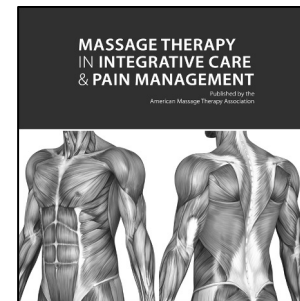
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Massage Therapy

- **Manual manipulation of soft tissue** intended to promote **health and well-being.**
- Key component of **pain management, overall health, and wellness.**
- Incorporating into broader pain management plan can help both **chronic and acute pain.**
- Licensed massage therapists integrated into teams at Dana-Farber Cancer Institute, Memorial Sloan-Kettering Cancer Center, Mayo Clinic, Duke Health System, M.D. Anderson Cancer Center and many others.



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Evidence Based Massage Recommendations

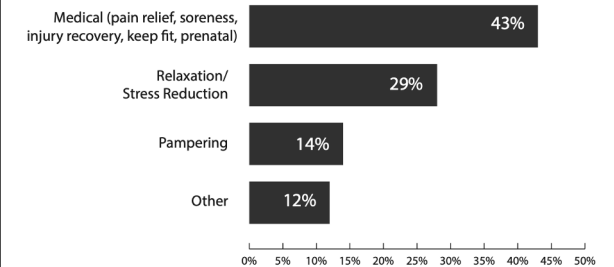
| CHRONIC PAIN MANAGEMENT (pages 9-11) | BEHAVIORAL HEALTH TREATMENT (pages 12-13) | CARE FOR REHABILITATION/ PHYSICAL TRAINING (pages 13-16) | ACUTE MEDICAL TREATMENT (pages 16-20) |
|---|--|--|--|
| Back pain | Anxiety and stress | Performance training/ injury treatment | Cancer management |
| Neck and shoulder pain | Depression | Ergonomics and job-related injuries | Post-operative pain |
| Headache | PTSD | Cardiac rehab | Lifestyle diseases |
| Carpal tunnel syndrome | Substance use disorder recovery | Joint replacement surgery | Maternity and newborn care |
| Osteoarthritis | | Scar management | |
| Fibromyalgia | | | |
| Hospice | | | |

https://www.amtamassage.org/globalassets/documents/publications-and-research/mt_in_integrative_care_and_pain_management.pdf, Accessed October 23, 2022

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Figure 1: Top Reasons for Getting a Massage in 2017



https://www.amtamassage.org/globalassets/documents/publications-and-research/mt_in_integrative_care_and_pain_management.pdf, Accessed April 22, 2022

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Examples of Different Massage Types

- **Swedish:** most common. Uses effleurage (long flowing strokes), petrissage (rolling, kneading), friction (deep, circular strokes), tapotement (tapping with cupped hand, hand edge). Relaxing.
- **Deep tissue:** slow deep strokes apply pressure to specific problem areas.
- **Sports:** variety of techniques promote flexibility, prevent injuries and/or promote recovery. Used before, during, after training.
- **Shiatsu:** uses rhythmic pressure on acupressure points.
- **Thai:** put into variety of positions to mobilize joints, compress muscles.
- **Pregnancy:** relieve swelling, stress, muscle and joint pain.

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Yoga Has Many Health Benefits

- Scientific evidence supports yoga for **stress management, mental health, mindfulness, healthy eating, weight loss and quality sleep.**
- Can improve **strength, balance and flexibility**, making it useful for all age but particularly elders
- American College of Physicians recommends as **first-line treatment for chronic low back pain.**

<https://www.hopkinsmedicine.org/health/wellness-and-prevention/9-benefits-of-yoga>

Cat Cow Pose

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Headaches

- Migraines/headaches ~ 13% of US population.
- Highest in women 18–44 yrs; 3-month prevalence of migraine or severe headache is roughly 26%.
- **Head pain third leading cause for ER visits.**
- **70% say headaches caused problems in relationships, 59% have missed family and social events, and 51% report that migraines cut their work and school productivity in half.**

Smitherman TA, et al. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. *Headache* 2013 Mar;53(3):427-36.

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Spinal Manipulation for Headaches

- **Cervicogenic headaches** are a common disorder.
- Systematic review found SMT provides **superior short-term effects for pain intensity, frequency and disability.**
- Spinal and cervical manipulation are included in numerous practice guidelines for **chronic neck pain and headache.**



Fernandez M, et al. *Eur J Pain* 2020 Oct;24(9):1687-1702.
Practice Guidelines *JOSPT* 2017; 47(7): 444-AR3

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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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Magnesium

- **Low magnesium** intakes and serum levels associated with **type 2 diabetes, metabolic syndrome, inflammation, high blood pressure, atherosclerotic vascular disease, sudden cardiac death, pain, osteoporosis, migraine, asthma, and colon cancer.**
- **50% of U.S. population** consumes less than the required amount of daily magnesium.
- Deficiency associated with negative effects on calcium and vitamin D homeostasis. **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 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.

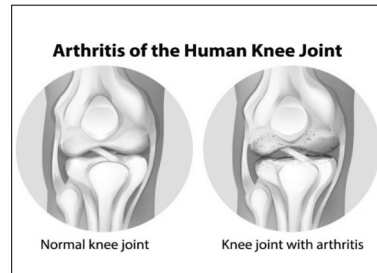
Shmigel A, et al. Low magnesium intake is associated with increased knee pain in subjects with radiographic knee osteoarthritis: data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2018 May;26(5):651-658; deOliveira GS, et al. Peri-operative systemic magnesium to minimize postoperative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

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Magnesium and Knee Pain

- Study **2,548 patients** over **4 years** found even after adjusting for countless variables (e.g., age, sex, BMI, pain med use, physical activity, kidney function, alcohol use, etc.)
...**low magnesium intake was strongly associated with worse pain and function** ($p < 0.001$).



Shmigel 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

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Magnesium for Migraines



- Studies show migraineurs have low brain Mg during migraine attacks and may have systemic Mg deficiency.
- Canadian Headache Society: **strong recommendation** for prophylaxis with **600 mg magnesium citrate**.
- Diarrhea most common side effect (mag **glycinate** and **citrate** less GI complaints than oxide). **L-threonate** perhaps best for migraine. Start with 300 mg/d.
- Caution in those with poor renal function.

Pringsheim T, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci* 2012; 39(2Suppl):S1-S9

Chiu HY, et al. Effects of Intravenous and Oral Magnesium on Reducing Migraine: A Meta-analysis of Randomized Controlled Trials. *Pain Physician* 2016; 19(1):E97-112.

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Riboflavin for Migraines



- CHS guidelines **gave strong recommendation for benefit, and minimal side effects**
- **Teenage girls often low in riboflavin**
- AAN/AHS give riboflavin Level B recommendation, **probably effective** and should be considered for migraine prevention, 200 mg BID
- **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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Ginger (*Zingiber officinale*)

- Study 60 adults at ER for **treatment of migraine** randomized to **400 mg ginger extract** (5% gingerol) or **placebo + 100 mg IV ketoprofen**.
- Patients filled out **headache diary** before, 0.5h, 1h, 1.5h, and 2h after medication. Severity, functional status, migraine symptoms recorded.
- **Ginger group** showed significantly better clinical response after 1 h ($p = 0.04$), 1.5 h ($p = 0.01$) and 2 h ($p = 0.04$); **pain reduction and improved functional status reported at all time points**.



Martins LB, et al. Double-blind placebo-controlled randomized clinical trial of ginger (*Zingiber officinale* Ros.) addition in migraine acute treatment. *Cephalgia* 2019; 39(1): 68-76

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Peppermint: Headache



- **Topical treatment with peppermint essential oil** shown significantly more effective than placebo in controlled studies.
- **Efficacy comparable to aspirin or acetaminophen.** Peppermint oil in ethanol licensed for treatment of tension-type headache in adults and children above 6 years in Germany.

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Anti-Inflammatory Herbs

Some to consider include:

- Salix rich plants, like willow (*Salix* spp)
- Turmeric (*Curcuma longa* and other species)
- Ginger (*Zingiber officinale*)
- Boswellia (*Boswellia serrata*)
- Cannabis (*Cannabis sativa*)
- Devil's Claw (*Harpagophytum procumbens*)
- Licorice (*Glycyrrhiza glabra*, *G. uralensis*)



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Willow Bark (*Salix* spp)



- Willow bark supplements are effective for minor pain. They deliver up to 240 mg of salicin, which can be metabolized to **113 mg salicylic acid**.
- Low-dose aspirin (62 mg of salicylic acid) must include guidelines on use in pregnant women/children; info on blood coagulation.
- These same considerations should be considered for standardized willow bark extracts.

Oketch-Rabah H, Marles RJ, Jordan SA, Low Dogg T. United States Pharmacopoeia Safety Review of Willow Bark *Planta Med* 2019; 85(16): 1192-1202

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Turmeric (*Curcuma longa*)

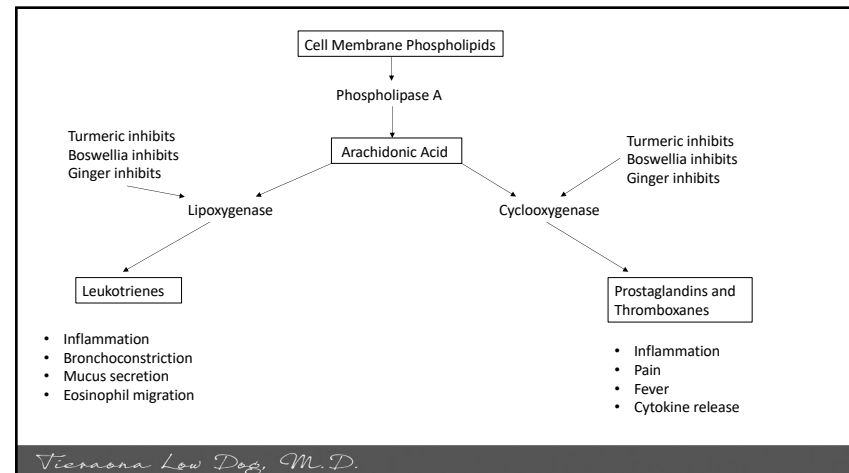
- Family: Zingiberaceae (ginger family)
- Part Used: Rhizome
- Perennial plant grown in tropical areas, mostly India. Used in meat, fish, and vegetable curries.
- Long history of medicinal use ~4,000 years.
- Curcuminoid pigments highly active; **curcumin** is the main curcuminoid.



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Turmeric Rhizome (*Curcuma longa*) Boswellia Gum Resin (*Boswellia serrata*)

- Curcumin and boswellia **significantly more effective than placebo for pain relief/functional improvement.**
- No significant differences between curcumin, boswellia and placebo in **safety outcomes.**
- **Curcuminoids** similar efficacy to NSAIDs; **significantly less likely** to experience gastrointestinal adverse events.
- “Curcumin and boswellia formulations could be valuable addition to knee OA treatment regimens by relieving symptoms while reducing safety risks.”



Bannuru RR, et al. Efficacy of curcumin and Boswellia for knee osteoarthritis: Systematic review and meta-analysis. *Semin Arthritis Rheum* 2018 Mar 10; pii: S0049-0172(18)30002-7

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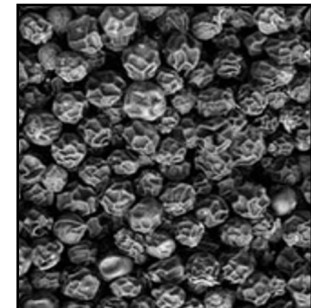
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"Cancer Prevention in 21st Century"

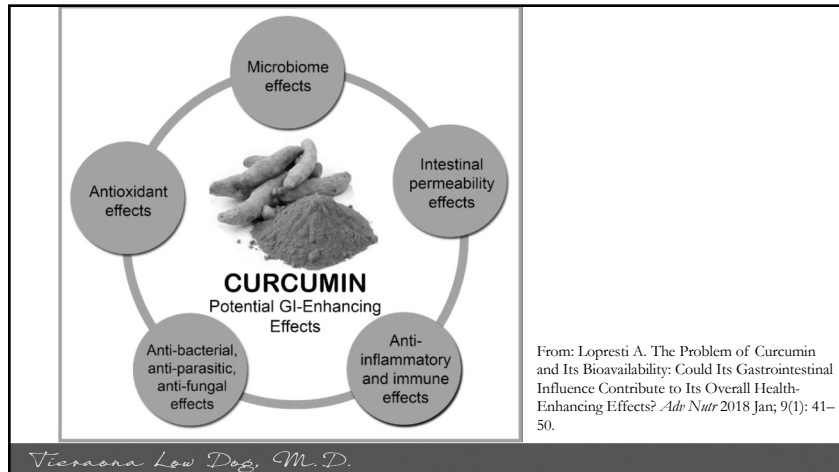
Absorption & Safety Issues

- **<1% curcumin reaches peripheral blood after oral ingestion even at high doses (12 grams).** Only organ exposed to high concentration is **gastrointestinal tract.**
- Preparations bound to **phosphatidylcholine (Meriva)** or **piperine (2–5 mg per 500 mg curcumin)** are thought to offer superior absorption.
- **Dose: 1,000–1,200 mg/d standardized extract (95% curcumin)** used in most of the trials.



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Temporomandibular Disorder

- Term used to group conditions in the **masticatory muscles and the temporomandibular joint (TMJ)**, impaired movement capacity of the mandible, and TMJ symptoms such as **clicking, grating and locking of the jaw**.
- Most common cause of chronic orofacial pain.

Okeson JP. *Management of temporomandibular disorders and occlusion*. 7 ed. Elsevier: Mosby; 2012.

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TMD: Significant Cause of Pain

- 5–12%** of population. **Second** most common musculoskeletal condition (after chronic low back pain) resulting in pain and disability.
- Arthralgia, local myalgia, myofascial pain, myofascial pain with referral, degenerative joint disease, subluxation, and headache.**

Manfredini D, et al. Research diagnostic criteria for temporomandibular disorders: a systematic review of axis I epidemiologic findings. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2011;112:453–462.

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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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Care Option



- Ice or heat applications
- Soft foods when pain acute
- Self-care exercises
- Physical therapy
- Splint
- Anti-inflammatory diet
- Topical analgesics (e.g., capsaicin)
- Acupuncture

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Splint vs. Self Exercise

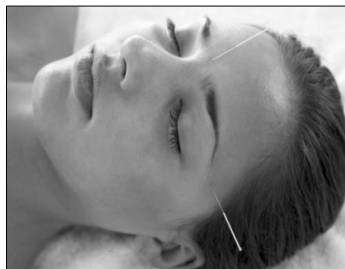
- 52 people anterior disc displacement without reduction randomly assigned to **splint** or a joint mobilization **self-exercise** treatment group.
 - Warm-up, small mouth-opening and closing movements several times. Then mandibular downward pressure: 3 cycles of 30 seconds each 4 times per day.
 - Participants in **splint group** wore a maxillary stabilization appliance while sleeping at night. Splint adjusted to ensure occlusal contact of all mandibular teeth in centric relation and mandibular canine guidance in eccentric movement.
- **All outcome variables significantly improved after 8 weeks of treatment** in both groups (mouth opening range, maximum daily pain intensity, limitation of daily functions). **Mouth opening range increased more in the exercise group than in the splint group.**

Haketa T, et al. Randomized Clinical Trial of Treatment for TMJ Disc Displacement. *Journal of Dent Res* 2010; 89(11):1259-63

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Acupuncture & TMD



Small studies show **dry needling or acupuncture of lateral pterygoid and posterior, periarticular connective tissue, masseter, and temporalis muscles improves pain and disability in those with TMD.**

Fernandes AG, et al. Acupuncture in Temporomandibular Disorder Myofascial Pain Treatment: A Systematic Review *J Oral Facial Pain Headache* 2017 Summer;31(5):225-232.

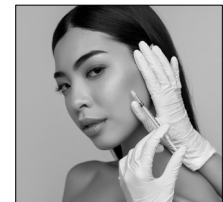
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Botox

- Systematic review 24 RCTs.
 - 9 used BTX injections to treat myofascial pain
 - 4 to treat (TMJ) articular TMDs
 - 8 for management of bruxism
 - 3 to treat masseter hypertrophy.
 - Wide variability in methods of injection and doses injected.
- Conclusion: there is good scientific evidence to support the use of BTX injections for treatment of masseter hypertrophy and equivocal evidence for myogenous TMDs, but very little for TMJ articular disorders.

Delcanho R, et al. *Journal of Oral & Facial Pain & Headache* 2022; 36(1):6-20



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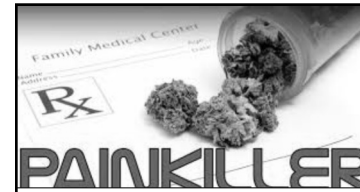
Topical Cannabidiol (CBD) for Pain

- **4-week study 29 patients** (mean 68 years) with **symptomatic peripheral neuropathy**. 15 patients randomized to CBD group (250 mg CBD/3 fl. oz) and 14 patients to placebo. **Statistically significant reduction in intense and sharp pain, cold, itchy sensations in CBD group compared to placebo.**
- **14-day study 60 patients with TMD:** randomized to **topical CBD (1.46%) or placebo** applied to **masseter muscles BID**. Compared to baseline, sEMG masseter activity significantly decreased CBD group (11% right and 12.6% left masseter muscles) vs. (0.23% right and 3.3% left) placebo group. **Pain reduced 70% in CBD group versus 9.8% in placebo group.**

Xu DH, et al. The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities. *Curr Pharm Biotechnol* 2020;21(5):390-402.
Nitecka-Buchta A, et al. Myorelaxant Effect of Transdermal Cannabidiol Application in Patients with TMD: A Randomized, Double-Blind Trial. *J Clin Med* 2019; 6(8):1886.

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Cannabis & Pain

- Systematic review and meta-analysis of cannabinoids: **28 RCTs (2,454 patients) with chronic pain found that, compared with placebo, cannabinoids associated with greater reduction in pain.**
- Cannabis containing THC provides **greater analgesia.**
- Dosing remains confusing. Note: Most studies of CBD used 300 mg per day, far greater than what is commonly used.

Whiting PE, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313:2456-2473

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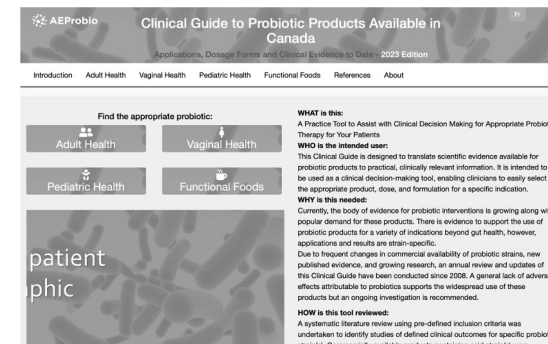
Microbiota-Gut-Pain

- Gut health characteristics that contribute to well-being: **digestion and absorption of food, normality of GI microbiota, immune function, and absence of GI disease.**
- **Dysbiosis** associated with **visceral pain** disorders such as **IBS, functional dyspepsia, functional abdominal pain syndrome, infant colic.**
- Microbial manipulation using **prebiotics and probiotics** shows therapeutic promise. Microbial manipulation also shows promise for secondary gains in improved mood or symptom control.

Pasceddu MM, Gareau MG. Visceral pain: gut microbiota, a new hope? *J. Biomed. Sci.* 2018; 25(1), 73
Cenit MC, et al. Influence of gut microbiota on neuropsychiatric disorders. *World J. Gastroenterol* 2017; 23(30), 5486-5498
Guo R, et al. Pain regulation by gut microbiota: molecular mechanisms and therapeutic potential. *BJA* 2019; 123(5): 637-54

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www.probioticchart.ca

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Peppermint Leaf Essential Oil IBS

- **Meta-analysis RCTs:** soluble fiber, antispasmodic drugs, peppermint oil, and gut-brain neuromodulators for IBS.
- **Peppermint oil ranked first for efficacy when global symptoms were used as the outcome measure,** and tricyclic antidepressants were ranked first for efficacy when abdominal pain was used as the outcome measure.
- **Dose 0.2 ml taken 2–3 times daily.**



Black CJ, et al. *Lancet Gastroenterol Hepatol*. 2019 Dec 16. pii: S2468-1253(19)30324-3.

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Think More Broadly

An integrated approach will move beyond the pain and explore...

- **Sleep and Rest**
- **Energy/Fatigue**
- **Work/Career/School**
- **Diet and Food**
- **Relationships**
- **Mind-Body**
- **Meaning and Purpose**



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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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The Basics for Sleep

1. Set a **sleep schedule** and stick to it.
2. Make your bedroom **dark, quiet and cool**.
3. Turn off electronics and or use **blue light blocking technologies**.
4. Watch the **caffeine**. Discontinue by noon if trouble sleeping.
5. **Power naps:** can be good if 20–30 minutes in duration.
6. **Limit alcohol** intake.
7. **Don't go to bed hungry**.
8. Find ways to **deal with “worries”**...
9. Get **sleep evaluation** if sleep disruption and/or daytime fatigue continues.
10. **Controlled-release melatonin** recommended as first-line agents in older adults. (**2 mg sustained release** for 4–6 weeks and re-evaluate).

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Melatonin Sleep and Safety

- Meta-analysis: **12 randomized, placebo-controlled trials** found convincing evidence melatonin reduces time it takes to fall asleep in **primary insomnia** ($p = 0.002$) and **delayed sleep phase syndrome** (when it takes 2 or more hours to fall asleep past conventional bedtime) ($p < 0.0001$).
- Oral melatonin **reduces length of time needed to fall asleep**; advancing sleep onset time in **young adults and children with delayed sleep phase syndrome**.
- Studies **failed to show any serious adverse effects**, even at extreme doses (100 mg) in adults. Doesn't suppress endogenous production of melatonin and no rebound insomnia when discontinued.
- **Dose generally 2–3 mg 2 hours before bed.**



Auld F, et al. Evidence for the efficacy of melatonin in the treatment of primary adult sleep disorders. *Sleep Med Rev* 2017 Aug;34:19-22.
 Andersen LP, et al. The Safety of Melatonin in Humans. *Clin Drug Invest* 2016 Mar;36(3):169-75.
 McDougall MS, et al. Pharmacologic Treatments for Sleep Disorders in Children: A Systematic Review. *J Child Neurol* 2019 Apr;34(5):237-247.

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Melatonin and Pain

- Melatonin maintains sleep-wake cycle, acts as an antioxidant, **anti-inflammatory, pain reliever, and mood regulator**, making it ideal for many with chronic pain.
- Systematic review **19 studies**: significantly **decreases pain intensity**, regardless of the type of pain.
- Plays important role in GI physiology: regulation of gastrointestinal motility, local anti-inflammatory reaction and moderation of visceral sensation. Studies show it **can improve symptoms and quality of life in people living with IBS**.

Cheatle MD, et al. *Sleep Medicine Clinics*, 2016;11(4): 531-541; Zhu C, et al. *Oncotarget* 2017 Nov 21; 8(59): 100582–100592.

Esteban-Zubero E, et al. *Life Sci* 2017 Feb 1;170:72-81

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Cognitive Behavioral Therapy

- Recommended **first-line therapy** for insomnia. Digital CBT can be effective for improving sleep, as well as mental health and well-being.
- CBT-I typically consists of:
 - Psychoeducation about sleep and insomnia
 - Stimulus control
 - Sleep restriction
 - Sleep hygiene
 - Relaxation training
 - Cognitive therapy
- Sleepio, CBT-I Coach (free)

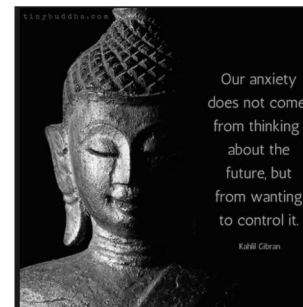


Luik AI, et al. Digital cognitive behavioral therapy for insomnia: a state of the science review. *Curr Sleep Med Rep* 2017; 3(2): 48–56

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Meditation



- Meditation is a mind-body practice with a long history of use for increasing **calmness and physical relaxation**, improving **psychological balance, coping with illness**, and enhancing overall **health and well-being**.
- It's about learning to **observe thoughts and feelings without judging them**.

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Meditation for Health

- Excellent for **reducing stress perception** and **pain intensity**, while **elevating mood**.
- Long-time meditators have greater activation of areas responsible for **sustaining attention, processing empathy, integrating emotion and cognition**.
- Review of **47 trials** found that meditation improves:
 - **Anxiety**
 - **Depression**
 - **Pain**



Goyal M, et al. *JAMA Intern Med* 2014; 174(3):357-68

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Resources for Stress Reduction

- **Calm** - Great app for guided meditation, bedtime stories, breathing exercises. (free to \$60 annual subscription)
- **Insight Timer** - ~4,000 guided meditations >1,000 teachers (self-compassion, nature, stress, podcasts). Music tracks (free to \$5/mo.)
- **Headspace** - Meditation, videos, meditations music. (free basic course, \$12.99 mo., \$95/year)
- **10% Happier** - Performance enhancement. Busy people, stressed lives. (free one-week intro, then \$100 per year)
- **Buddhify** - For more advanced meditator. Can sort by location, activity and/or emotion. (small monthly fee, premium is \$30/yr.)

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Meaning & Purpose

- What truly gives a person a sense of *meaning and purpose* in life?
- How can one discover their life purpose to focus on the essence of who they are—their *be-ing*?
- How can one live from a “*deep place*” despite their pain?
- So important to explore and is often the key to *less suffering*.

Listen.
Are you
breathing
just a little
and calling
it a life?

~ Mary Oliver

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Thank You!



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