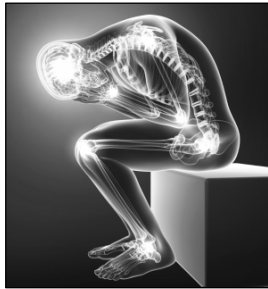


An Integrative Approach to Pain



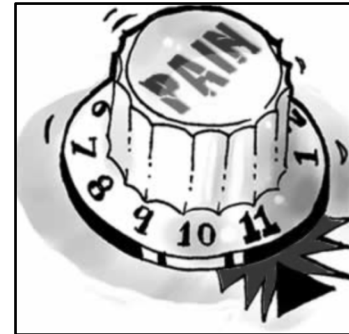
Tieraona Low Dog, MD

Chair: US Pharmacopeia Dietary Supplements
Admissions Joint Standard Setting Sub-Committee

Author of National Geographic's
"Fortify Your Life", "Healthy At Home"
and "Life Is Your Best Medicine"

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Pain



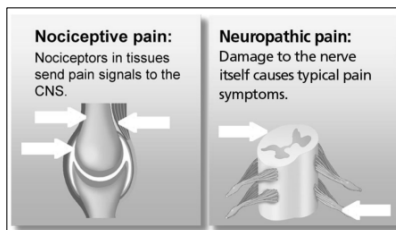
- Affects **>100 million Americans**, more than those with heart disease, cancer, and diabetes combined.
- **25.3 million adults suffer from daily chronic pain, while 23.4 million report severe pain.**
- Incidence of chronic low **back pain**, **neck pain**, and **arthritic pain** as high as 29%, 15.7%, and 28%, respectively, in adult population.

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

Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *J Pain* 2015 Aug;16(8):769-80.

Tieraona Low Dog, M.D.

Chronic Pain



- Complex, severe and debilitating condition - considerable reduction in function & quality of life.
- Pain due to dysfunction of nerves, spinal cord or brain (neuropathic pain), or persistent pain caused by other non-malignant conditions, such as low-back pain or pain due to inflammation of various arthritic conditions.

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Neuropathic Pain

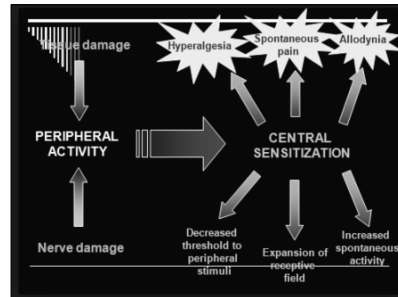
- Pain arising as a direct consequence of a lesion or disease of the somatosensory system (essentially all sensory experiences other than vision, hearing, taste and smell).
- Trauma, poorly controlled diabetes, side effect from drugs, infections (e.g., HIV, shingles), and autoimmune conditions (e.g., multiple sclerosis) can all lead to neuropathic pain. Rates can be high in some populations.
- Primarily managed: antidepressants, anticonvulsants, opioids, and topical agents.
- Neuropathic pain can be particularly difficult to treat and is often accompanied by anxiety, depression, insomnia, and fibromyalgia.

DiBonaventura MD, et al. The prevalence of probable neuropathic pain in the US: results from a multimodal general-population health survey. *J Pain Res* 2017; 10: 2525-2538.

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Central Sensitization

- Heightened sensitivity to pain and sensation of touch (also to other senses like light or sound).
- Nervous system in persistent state of heightened reactivity - simple touch can be registered as painful or uncomfortable even when it shouldn't.
- Increases feelings of anxiety, emotional distress, malaise, and poor concentration.



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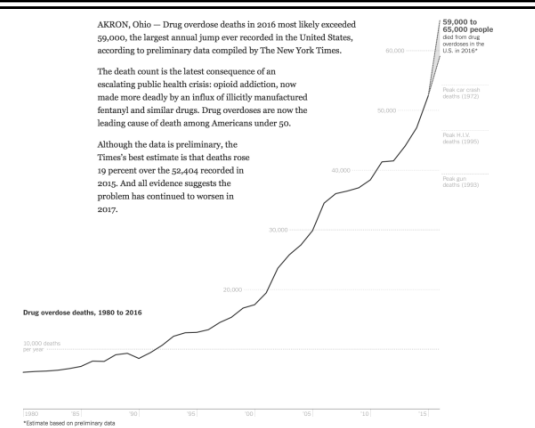
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Opiates

- Opioid industry more than \$13 billion-a-year. Americans **comprise ~4% of the world's population, we use > 30% of all opioids**. US accounts for ~100% of hydrocodone (e.g., Vicodin), 81% for oxycodone (e.g., Percocet).
- **91 Americans die** every day from opioid overdose; 50% from prescription opiates.
- Clinicians ill-prepared to deal with complex problems associated with chronic pain and are crunched by time, creating an easy atmosphere for prescribing pain meds.
- Pharmaceutical companies pumped millions of dollars into telling health professionals and public that these medications were safe and effective for chronic pain, claims that are now being challenged in courtrooms across the US.

Haffajee RI, et al. Drug Companies' Liability for the Opioid Epidemic *N Engl J Med* 2017; 377:2301-2305

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"Drug Deaths in America Are Rising Faster Than Ever"

Josh Katz, *NY Times* June 5, 2017

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The Down Side to Long-Term Use

- Opioids incredibly effective for **short-term pain relief** but risks often outweigh benefits for many people living with chronic pain.
- Review found for chronic non-cancer pain the absolute event rate for **any adverse event with opioids** in trials using a placebo as comparison was **78% with medium and long term use (average 6-16 weeks)**.
- These included **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 and Naproxen

- Large-scale Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen (PRECISION) trial and individual patient data of nearly 500,000 patients concluded “the evidence **would support avoidance of NSAID use, if possible, in patients with, or at high risk for, cardiovascular disease.**”
- If used, the **shortest-duration and lowest effective NSAID dose** should be chosen, given evidence that risk is duration- and dose-dependent.”
- The study found that **ibuprofen** use was associated with a **significant increase in systolic blood pressure** and higher incidence of newly diagnosed hypertension.

Pepine CJ, et al. Cardiovascular safety of NSAIDs: Additional insights after PRECISION and point of view. *Clin Cardiol* 2017 Dec;40(12):1352-1356.

Ruschitzka F, et al. Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial. *Eur Heart J* 2017 Nov 21;38(44):3282-3292.

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Ibuprofen and Heart Disease

- FDA warning about NSAID use in patients with cardiovascular disease (CVD) was released in 2005 and strengthened in July 2015, yet survey data shows that 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 and GI Bleeding



- Systematic review found low dose aspirin associated with **double the risk for upper GI bleeding and 80% increased risk for lower GI bleeding.**
- With increased risk from low-dose aspirin (81-85 mg per day), deeply concerning about long-term use of higher dose aspirin (2000-3000 mg per day) used for pain.
- PPI can protect against bleed but comes with own risks.

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.

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Acetaminophen (Paracetamol)



- Acetaminophen has superior safety profile to ibuprofen, naproxen, and aspirin; commonly recommended as a first line therapy for pain.
- **Maximum “safe” dose is 4000 mg per day** but found in more than 600 OTC and prescription medications (e.g., Vicodin), dose can add up without realizing it.

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

Walter RB, et al. Long-term use of acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs and risk of hematologic malignancies: results from the prospective Vitamins and Lifestyle (VITAL) study. *J Clin Oncol* 2011; 29(17):2424-31.

Adverse Effects

- 2017 report found acetaminophen responsible for nearly half of acute liver failure cases in US - **leading cause of liver transplantation.**
- Study of 64,839 men and women (ages 50-76 years) followed for up to 8 years found almost **two-fold increased risk of blood cancers associated with high use of acetaminophen (≥ 4 days/week for ≥ 4 years).**

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Blunts Empathy?

- Ohio State University research found in healthy college students, acetaminophen reduces user's ability **to feel empathy for another's pain.**
- This research must be confirmed by larger studies but hard not to find the researcher's statement somewhat chilling:
 - **"Because empathy regulates prosocial and antisocial behavior, these drug-induced reductions in empathy raise concerns about the broader social side effects of acetaminophen, which is taken by almost a quarter of adults in the United States each week."**

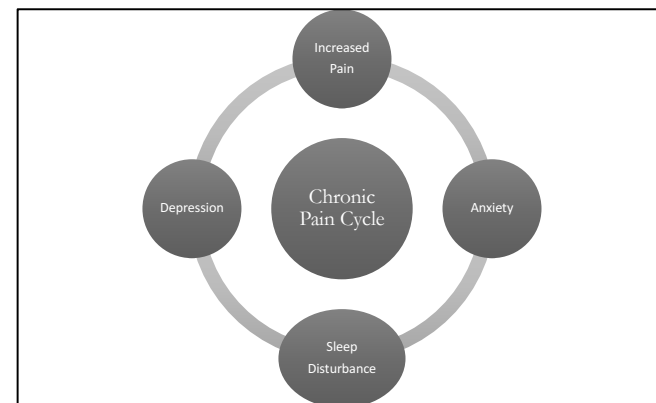
Mischkowski D, et al. From painkiller to empathy killer: acetaminophen (paracetamol) reduces empathy for pain. *Soc Cogn Affect Neurosci* 2016 Sep;11(9):1345-53.

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The Need for Alternatives

- There is keen interest by researchers, clinicians and the public for additional/other options for managing chronic pain.
- **Chronic pain is the leading indication for use of complementary and integrative medicine with 33% of adults and 12% of children in the US using it for this purpose.**
- Although advances have been made in treatments for chronic pain, it remains inadequately controlled for many people.

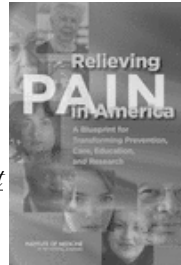
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IOM Report

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

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A Broader Approach

- Truly integrated approach would include treatments that address **mind-body** (e.g., meditation, yoga, tai-chi), **nutrition** (e.g., emphasis on plant based diet to reduce inflammation), **manual medicine** (e.g., massage, chiropractic), **pain modulation** (e.g., acupuncture, massage, botanicals, nutraceuticals), **sleep and mood** (e.g., cognitive behavioral therapy, guided imagery, botanicals, nutraceuticals).



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Where Are They, Where Do They Want to Go



- An integrated approach will move beyond the pain and explore....
 - **Sleep and Rest**
 - **Work/Career**
 - **Diet and Food**
 - **Relationships**
 - **Mind-Body**
 - **Meaning and Purpose**

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The Role of Diet in Pain



- Role of diet recognized in numerous pain conditions but likely contributes to many pain disorders:
 - Irritable bowel syndrome
 - Inflammatory bowel disease
 - Migraine (food triggers, as well as fasting induced headaches)

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Dietary Inflammatory Index (DII)

- Inflammation in body often driven by eating a **pro-inflammatory dietary pattern**. Inflammatory mediators can impact pain, mood, heart disease, insulin sensitivity, and DNA repair.
- The test can be downloaded as an app: **Dietary Inflammatory Index (DII Screener)**.
- Patients can take the test and there is mechanism for them to submit the results to you.

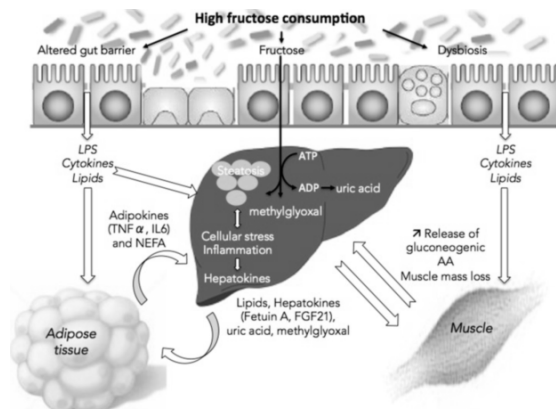
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Inflammatory Food Ratings

200 or higher	Strongly anti-inflammatory
101 to 200	Moderately anti-inflammatory
0 to 100	Mildly anti-inflammatory
-1 to -100	Mildly inflammatory
-101 to 200	Moderately inflammatory
-201 or lower	Strongly inflammatory

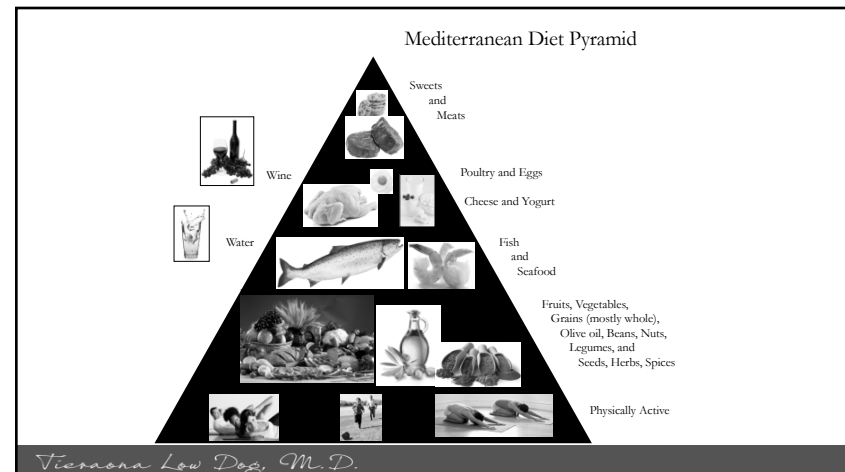
FOOD	SERVING SIZE	SERVING SIZE (GRAMS)	IF RATING
AGAVE NECTAR	1 TBSP	21	-74
ALMOND BUTTER	¼ CUP	64	100
CHEESE, CHEDDAR	1 OUNCE	28.35	-20
CHICKEN BREAST, RSTD	3 OUNCES	85	-19
MILK, WHOLE	1 CUP	246	-46
OLIVE OIL	1 TBSP	14	74
ONIONS, COOKED	½ CUP	105	240
RICE, WHITE	1 CUP	158	-153
SPINACH	1 CUP	30	75
SALMON, SOHO BAKED	3 OUNCES	85	450
TURMERIC	½ TSP	1.5	338

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Jegatheesan P, et al. Fructose and NAFLD: The multifaceted aspects of fructose metabolism. *Nutrients* 2017; Mar 3;9(3)

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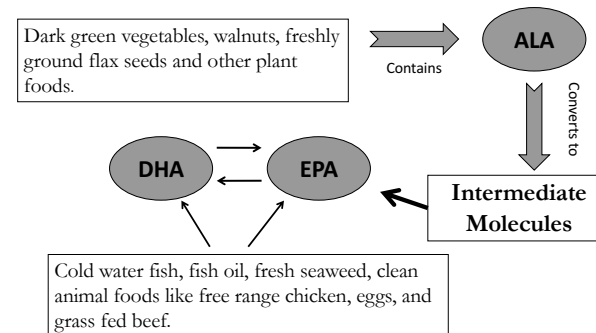
Mediterranean Dietary Pattern

- 13 meta-analyses of observational studies and 16 meta-analyses of randomized controlled trials investigating the association between the adherence to the Mediterranean diet and 37 different health outcomes, for a total population of over than **12,800,000 subjects, were reviewed.**
- Robust evidence (P-value<0.001) and large sample sizes showed that greater adherence to the Mediterranean diet was associated with *reduced risk of overall mortality, cardiovascular diseases, myocardial infarction, overall cancer incidence, diabetes, and neuro-degenerative diseases. Inflammatory mediators consistently reduced.*

Dinu M, et al. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomized trials. *Eur J Clin Nutr* 2017; May 10. doi: 10.1038/ejcn.2017.58.

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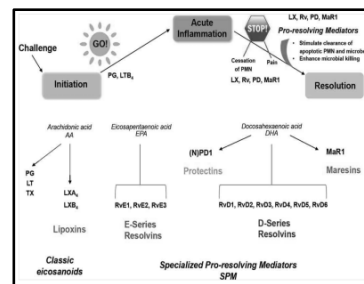
Omega 3 Fatty Acids from Plants and Animals



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Resolution Biology

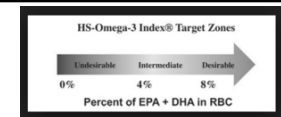
- Research shows that resolution of inflammation is an active, programmed response.
- Omega 3 fatty acids produce specialized **pro-resolving mediators** (SPM) – resolvins, protectins and maresins.
- Increasing omega 3 fatty acids in the diet can help with mood, pain and promote overall health.



Serhan CN, Chiang N. *Curr Opin Pharmacol* 2013; 13(4):632-40

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Canadians and Omega 3



- Omega-3 Index indicates % of EPA+DHA in red blood cell fatty acids.
- Canadian government found the mean Omega-3 Index level of Canadians aged 20-79 was 4.5%. Fewer than 3% of adults had levels associated with low CHD risk; 43% had levels associated with high risk.
- **What about chronic pain patients? Should we assess omega 3 fatty acid level to optimize their “anti-inflammatory” activity?**

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

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Choose Your Seafood Wisely

The Seafood Watch App

Available for iOS and Android

It's easier than ever to get the latest recommendations for seafood and sushi, learn more about the seafood you eat, and locate or share businesses that serve sustainable seafood.

Download on the App Store | GET IT ON Google play

View our App FAQs

Features

- Get free, up-to-date seafood recommendations
- Search for seafood quickly and easily by common market name
- Search for sushi by Japanese name as well as common market name
- Find restaurants and stores near you that serve ocean-friendly seafood
- Access in-depth conservation notes and reports

<https://www.seafoodwatch.org/seafood-recommendations/our-app>

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Fish Oil: What Type is Best?

- Supplementation is an alternative to eating fish; however, not all supplements are equal.
- Randomized, crossover study of 35 healthy individuals compared four popular brands/types of omega 3 fatty acids:
 - Concentrated triglyceride (rTG)
 - Ethyl ester (EE)
 - Phospholipid krill oil (PL)
 - Triglyceride salmon oil (TG)

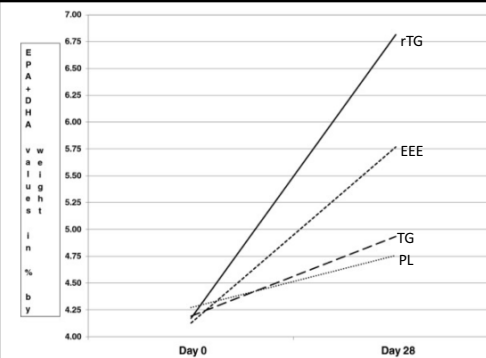
Laidlaw M, et al. *Lipids Health Dis* 2014; 13:99

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Dosing According to Manufacturer's Recommendations

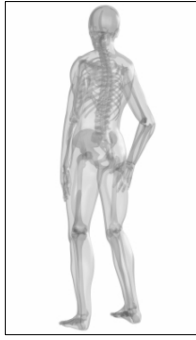
TRT	Product	EPA & DHA per capsule*	Tested values	Label use: caps/day	Daily dosage of EPA + DHA
rTG	Nordic Naturals ProOmega®	325 mg EPA	329.6 mg EPA	2	EPA: 650 mg
	Triglyceride	225 mg DHA	226.0 mg DHA		DHA: 450 mg
EE	Minami MorEPA®	756 mg EPA	774.2 mg EPA	1	EPA: 756 mg
	Platinum Ethyl Ester	228 mg DHA	233.7 mg DHA		DHA: 228 mg
PL	Source Naturals ArcticPure®	75 mg EPA	78.0 mg EPA	2	EPA: 150 mg
	Krill Oil Phospholipid	45 mg DHA	46.7 mg DHA		DHA: 90 mg
TG	New Chapter				
	Wholemega® Salmon	90 mg EPA	96.4 mg EPA	2	EPA: 180 mg
	Oil Triglyceride	110 mg DHA	109.5 mg DHA		DHA: 220 mg

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Mean levels of EPA + DHA for four supplement groups at Day 0 and Day 28.

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Musculoskeletal Pain

- Musculoskeletal conditions **are leading cause** of long-term pain and disability around the globe.
- **Aging, obesity and lack of regular physical activity** are major risk factors for arthritis and back pain.
- In US, 52 million American adults have arthritis and by **2040, that number will reach 78.4 million, or roughly 26% of all adults.**

Hootman JM, et al. Updated Projected Prevalence of Self-Reported Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation Among US Adults, 2015-2040. *Arthritis Rheumatol* 2016 Jul;68(7):1582-7.

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Body Weight

- For every **12 pounds of weight gain, there is a 36% increased risk for developing OA.**
- Lumbar spine and knee two primary sites for pain in obese individuals. Reduction of body fat lowers mechanical and inflammatory stressors that contribute to OA.
- **Weight loss strongly associated with a reduction in pain.**

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Anti-Inflammatory Herbs

- There are many, but some to consider include:
 - Salix containing plants
 - Turmeric (*Curcuma longa* and other species)
 - Ginger (*Zingiber officinale*)
 - Boswellia (*Boswellia serrata*)
 - Chinese skullcap (*Scutellaria baicalensis*)
 - Devil's Claw (*Harpagophytum procumbens*)
 - Cat's Claw (*Uncaria tomentosa*)
 - Licorice (*Glycyrrhiza glabra*, *G. uralensis*)

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Turmeric (*Curcuma longa*)

- Family: Zingiberaceae (ginger family)
- More than 130 species worldwide
- Part Used: Rhizome
- Perennial plant grown in tropical areas, most grown in India, they consume 80% of crop. Used in meat, fish and vegetable curries.
- Long history of medicinal use ~4,000 years.
- In ancient Ayurvedic literature, called Jayanti, meaning "one who is victorious over disease."

www.ncbi.nlm.nih.gov/books/NBK92752/ Accessed September 2, 2018



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Turmeric: the Curcuminoids

- Among 300 compounds in turmeric are curcuminoid pigments.
- **Curcumin (diferuloylmethane)** is the main curcuminoid.
- Other compounds in whole rhizome aid in absorption (more later).



Gupta S, et al. Curcumin, a Component of Turmeric: From Farm to Pharmacy. *Biofactors* 2013; 39(1):2-13

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Turmeric for Arthritis

- Profound anti-inflammatory effects; studies show turmeric reduces pain in rheumatoid and osteoarthritis.
- Systematic review concluded that RCTs of turmeric/curcumin provide evidence that **supports the efficacy of turmeric extract in treatment of arthritis equivalent to pain medications.**



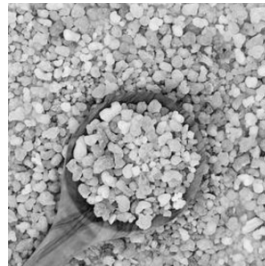
Chen K-Y. *Drug Deliv Ther* 2016; 10: 3029-3042

Pedlada KV, et al. *Orth Surg* 2015; 7(3):222-31

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Turmeric + Boswellia (*Boswellia serrata*)

- **12 week randomized, double-blind, placebo controlled study in 201 people with osteoarthritis (40-70 years of age)** found that **350 mg curcuminoids + 150 mg boswellic acid** taken **three times daily** led to statistically significant effect on physical performance tests and WOMAC joint pain index compared to placebo. Well tolerated, no significant adverse events.



Haroyan A, et al. Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study. *BMC Complement Altern Med* 2018 Jan 9;18(1):7.

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Review on Turmeric and Boswellia

- Tuft's systematic review 11 RCTs. Both curcumin and boswellia formulations statistically significantly more effective than placebo for **pain relief and functional improvement.**
- **Curcumin showed no statistically significant differences in efficacy outcomes compared to NSAIDs;** patients on curcumi significantly less likely to experience gastrointestinal adverse events.
- Results suggest **curcumin and boswellia formulations could be valuable addition to 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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Turmeric: Cardiovascular

- **Meta-analysis 20 studies** found a significant decrease in **serum triglycerides and elevation of HDL-C**.
- A 12 week randomized, placebo controlled trial in 118 people with type-2 diabetes found that **1000 mg curcumin + 10 mg piperine/d** led to **significant reduction in serum total cholesterol, non-HDL-C and lipoprotein (a)**

Simental-Mendia LE, et al. Lipid-modifying activity of curcuminoids: A systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr* 2017 Nov 29;1-10.

Panahi Y, et al. Curcuminoids modify lipid profile in type 2 diabetes mellitus: A randomized controlled trial. *Complement Ther Med* 2017 Aug;33:1-5.

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Depression and Pain

- Multiple studies suggest a link between inflammation, depression and pain.
- Danish study (>73,000 adults) showed that those with the **highest levels of C-reactive protein (marker of inflammation)** were **twice as likely to have psychological distress and depression** than those with normal levels.



Wium-Anderson MK, et al. Elevated C-reactive protein levels, psychological distress, and depression in 73,131 individuals. *JAMA Psychiatry* 2013; 70(2):176-184

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Turmeric for Depression?

- Mini meta-analysis of 6 studies found curcumin **reduced depression symptoms**, particularly in middle-aged patients when given at higher doses for longer periods of time.
- Authors concluded, **“there is supporting evidence that curcumin administration reduces depressive symptoms in patients with major depression.”**
- Is it due to systemic reduction in inflammation?



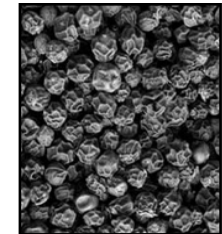
Al-Kawari D, et al. The Role of Curcumin Administration in Patients with Major Depressive Disorder: Mini Meta-Analysis of Clinical Trials. *Phytother. Res* 2016; 30(2):175-83

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“Cancer Prevention in 21st Century”

Absorption and Safety Issues

- Turmeric/curcumin not well absorbed into bloodstream from GI tract and what is absorbed is quickly metabolized and eliminated from the body.
- Best to take turmeric/curcumin 2-3 times per day, rather than once per day, for best effects.
- Preparations bound to **phosphatidylcholine** or include **piperine**, an alkaloid from black pepper, are optimal forms for pain.
- Dose of **1200-1500 mg per day of extracts standardized to curcumin** have been used in most of the trials.



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Ginger (*Zingiber officinale*)

- Meta-analysis comparing ginger with placebo in OA patients found “**Ginger was modestly efficacious and reasonably safe for treatment of osteoarthritis.**”
- Studies show beneficial effect on lipids/glucose.
- **1-2 grams/d dried rhizome has not been associated with adverse effects.**
- Doses higher than 4 grams per day can have a negative impact on blood clotting.



Wang J, et al. Beneficial effects of ginger *Zingiber officinale* Roscoe on obesity and metabolic syndrome: a review. *Annals of the New York Academy of Sciences* 2017; May 15. doi: 10.1111/nyas.

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- There are many ways to incorporate more turmeric into the daily diet as seen in my tips to the left.
- There are many recipes for golden milk – this is the one we use the most at my home.

Cannabis sativa



- Cannabis used to treat pain thousands of years.
- Major **psychotropic** component is Δ^9 -tetrahydrocannabinol (**THC**), one of 120 naturally occurring phytocannabinoids.
- **Cannabidiol (CBD) is another compound found in cannabis.** Does not produce euphoric effects but has antipsychotic, anxiolytic, anti-seizure, analgesic, and anti-inflammatory properties.

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Cannabis and Pain

- Systematic review and meta-analysis of cannabinoids: 28 RCTs (2454 patients) with chronic pain found that, compared with placebo, cannabinoids associated with greater reduction in pain.
- Legal issues remain a challenge for making THC rich cannabis and non-euphoric CBD products available more widely to patients.

Whiting PF, 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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Back Pain

- Lower back pain highly disruptive, **second leading cause of disability**.
- It is acute if less than six weeks and chronic if persists > three months.
- Pain can be severe, making walking, standing and traveling long distances difficult, even though physical activity is effective for improving and preventing back pain.
- Back pain is frequently associated with anxiety, depression and irritability.
- Second major cause of short-term workplace absences; estimated 149 million days of work per year lost due to low back pain.

Freburger JK, et al. The Rising Prevalence of Chronic Low Back Pain. *Arch Intern Med*. 2009 Feb 9; 169(3): 251–258.

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Clinical Practice Guidelines Back Pain

- American College of Physicians guideline is to provide **treatment guidance based on the efficacy, comparative effectiveness, and safety of noninvasive pharmacologic and nonpharmacologic treatments for acute (<4 weeks), subacute (4 to 12 weeks), and chronic (>12 weeks) low back pain in primary care.**
- **Recommendations are on following slides.**

Qaseem A, et al. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Annals of Internal Medicine* 2017;166(7):514-530.

Victoria Low Dog, M.D.

Acute or Subacute Low Back Pain: Guidance



- Given that most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select non-pharmacologic treatment with **superficial heat, massage, acupuncture, or spinal manipulation.**
- If pharmacologic treatment is desired, clinicians and patients should select NSAID or skeletal muscle relaxants
(Grade: strong recommendation)

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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.**



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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Chronic Low Back Pain Guidance

- Clinicians and patients should initially select non-pharmacologic treatment **with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, tai chi, yoga, progressive relaxation, electromyography biofeedback, cognitive behavioral therapy, or spinal manipulation**

(Grade: strong recommendation)



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Headaches

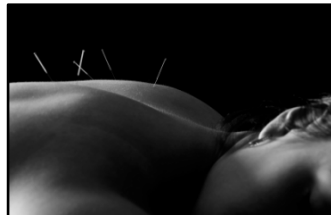
- Migraines/headaches significant source of pain, ~ 13% of US population.
- Burden of headache is highest in women ages 18-44, where 3-month prevalence of migraine or severe headache is roughly 26%. **Head pain is the third leading cause for emergency room visits.**
- Surveys show 70% of those with migraines say headaches have 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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Acupuncture for Migraine

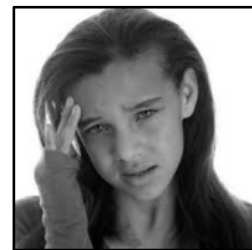
- Cochrane review 22 trials (n=4985) concluded that evidence suggests adding acupuncture to symptomatic treatment of attacks reduces frequency of headaches. Trials also suggest that **acupuncture may be at least similarly effective as treatment with prophylactic drugs.**
- “Acupuncture can be considered 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 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. AAN/AHS gave level B recommendation (**probably effective**).
- Diarrhea most common side effect (magnesium glycinate and citrate less GI complaints than oxide). Caution in those with poor renal function.

Pringsheim T, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci* 2012; 30(Suppl):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):107-112.

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Coenzyme Q10 for Migraines

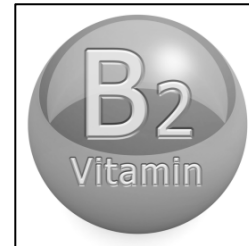


- CHS guidelines gave a **strong recommendation** for prophylaxis of migraine: 300 mg/d.
- The AAN/AHS gave a Level C recommendation, stating it is **possibly effective** and may be considered for migraine prevention.

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

Vicronna Low Dog, M.D.

Riboflavin for Migraines



- CHS 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. 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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Butterbur Extract for Migraines (*Petasites hybridus*)

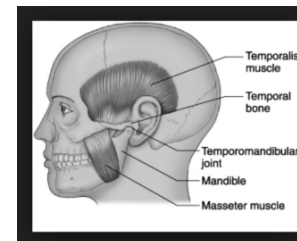
- Butterbur Level A recommendation for migraine prevention in adults from the AAN and AHS. CHS gave strong recommendation for migraine prophylaxis: 75 mg twice daily.
- These recommendations may be revised (but have not) due to several cases of liver damage reported in the literature. **Petadolex** is brand used in clinical trials.



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

Vicronna Low Dog, M.D.

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



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.

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

Vicanna Low Dog, M.D.

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
<small>Items 1 through 3A constitute the short version of the screening instrument, and items 1 through 10 constitute the long version. An a response receives 0 points, a b response 1 point and a c response 2 points.</small>	

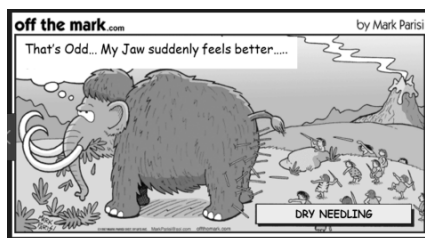
TMP Pain Screening Tool

- For clinical use, responses from the screener can be used as **part of the diagnostic 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.

Vicanna Low Dog, M.D.

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

Vicanna Low Dog, M.D.

Splint Versus Self Exercise

- 52 people with 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, individual placed fingertips on edge of mandibular anterior teeth and slowly pulled the mandible down until pain occurred on the TMJ-affected side. 3 cycles of 30 seconds each were done 4 times per day.
 - Participants in the **splint group** wore a maxillary stabilization appliance while sleeping at night. Splint was 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 with and without pain, maximum daily pain intensity, limitation of daily functions. In particular, the 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

Vicanna Low Dog, M.D.

Acupuncture and Dry Needling



- Small studies that used dry needling or acupuncture of the lateral pterygoid and posterior, periarticular connective tissue, masseter and temporalis muscles have shown improvements in pain and disability in patients with TMD.

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

Victoria Low Dog, M.D.

Mood, Sleep and Pain



- Depression and pain leading causes of global disability.
- Study of 273,952 individuals/47 countries found depression significantly associated with severe pain (odds ratio 3.93 (95% CI 3.54-4.37).
- High prevalence of concomitant pain and sleep disturbance and there is a bidirectional and reciprocal relationship.
- Pain can impair sleep but research also shows that insomnia and short sleep duration increases the risk for developing chronic pain.
- Study in healthy young women found after just two nights of fragmented sleep in an experimental setting, increased pain sensitivity in both superficial and deep tissues.

McWilliams LA, et al. A Network Analysis of Depressive Symptoms in Individuals Seeking Treatment for Chronic Pain. *Clin J Pain* 2017 Oct;33(10):899-904.
Iacovides S, et al. Sleep Fragmentation Hypersensitizes Healthy Young Women to Deep and Superficial Experimental Pain. *J Pain* 2017 Jul;18(7):844-854.

Victoria Low Dog, M.D.

Cognitive Behavioral Therapy

- CBT has emerged as a recommended first-line therapy for insomnia. Scale can be an issue. Digital CBT has been shown to 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

Victoria Low Dog, M.D.

Melatonin

- Melatonin maintains sleep-wake cycle, acts as an antioxidant, **anti-inflammatory, pain reliever, and mood regulator**, making it ideal for many with chronic pain.
- A systematic review of **19 studies** found that melatonin significantly **decreases the pain intensity**, as evidenced by pain scores, regardless of the type of pain.
- Plays important role in gastrointestinal 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. Assessing and Managing Sleep Disturbance in Patients with Chronic Pain. *Sleep Medicine Clinics*, 2016;11(4): 531-541
Zhu C, et al. Exogenous melatonin in the treatment of pain: a systematic review and meta-analysis. *Oncotarget* 2017 Nov 21; 8(59): 100582-100592.
Esteban-Zubero E, et al. Melatonin's role as a co-adjuvant treatment in colonic diseases: A review. *Life Sci* 2017 Feb 1;170:72-81

Victoria Low Dog, M.D.

Melatonin Sleep and Safety

- Meta-analysis of **12 randomized, placebo-controlled trials** found convincing evidence that melatonin reduced sleep onset latency (the 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) ($p < 0.0001$).
- Studies have **failed to show any serious adverse effects** with melatonin, even at extreme doses (100 mg) in adults. Taking melatonin doesn't suppress the endogenous production of melatonin and there is no rebound insomnia when it is discontinued. Dose generally 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;34:10-22.

Andersen LP, et al. The Safety of Melatonin in Humans. *Clin Drug Investig* 2016 Mar;36(3):169-75.

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Current Recommendations

- Controlled-release melatonin and doxepin are recommended as first-line agents in older adults; the so-called z-drugs (zolpidem, eszopiclone, and zaleplon) should be reserved for use if the first-line agents are ineffective.
- Dose generally 3-5 mg melatonin.



Matheson E, et al. Insomnia: Pharmacologic Therapy. *Am Fam Physician* 2017; Jul 1;96(1):29-35.

Vickianna Low Dog, M.D.

California Poppy (*Eschscholzia californica*)

- Official state flower California. Native Americans used as food and medicine for millennia.
- Aerial plant used to relieve tooth pain, headache, and promote sleep.
- Basic science shows it acts on **GABA-A receptors in the brain, similar to a benzodiazepine, but without habit-forming tendency of the drug. Has anxiolytic, analgesic, sedative activity.**



Fedurco M, et al. Modulatory Effects of *Eschscholzia californica* Alkaloids on Recombinant GABAA Receptors. *Biochem Res Int* 2015;2015:617620

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California Poppy

- **European Union monograph recognizes traditional use for relief of mild symptoms of mental stress and to aid sleep.**
- It also discusses research that indicates that a **"standardized extract of California poppy can be used in the management of chronic pain and as a hypnotic-mild-sedative for the management of pain-related insomnia."**
- Dose: 300-600 mg 1-2 times per day.



European Union herbal monograph on *Eschscholzia californica* Cham., herba. January 28, 2015
www.ema.europa.eu/docs/en_GB/document_library/Herbal_Community_herbal_monograph/2015/05/WC500186552.pdf

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Guided Imagery: *Imagine Yourself*.....

- An immersive, deeply relaxing intervention that uses calming words, soothing music and positive images to structure a healing experience.
- Like meditation, it focuses attention and calms the mind, working on those parts of the brain where the emotional self dwells.
- Imagery has been shown in clinical trials to reduce stress, anxiety, and depression; help with sleep; lower blood pressure, and help with posttraumatic stress.
- I have found guided imagery a fabulous tool for patients. Very helpful for those with anxiety, depression, pain, insomnia. And often an easier transition to meditation.

Victoria Low Dog, M.D.

Mindfulness Meditation

- Mindfulness meditation excellent as it can decrease pain intensity and stress levels.
- Long-time meditators have greater activation of areas responsible for sustaining attention, processing empathy, integrating emotion and cognition.
- Review of 47 trials found meditation improves:
 - Anxiety
 - Depression
 - Pain



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

Victoria Low Dog, M.D.

Meditation Resources

- Obviously a local class is the very best option. But there are books, CDS and yes, there are apps.....
 - Insight Timer - ~4,000 guided meditations from more than 1,000 teachers (self-compassion, nature, stress, podcasts and more). More than 750 meditation music tracks. Free.
 - Headspace – very good for beginners with 10 minute meditations. Free.
 - The Mindfulness App – nice 5 days guided mediation program to get you started. Can be personalized and integrated into other health apps. Free.
 - Aura – multiple teachers, from 3-10 minute daily meditations. Customizable. #1 new app on Apple. \$29 for 6 months.

Victoria Low Dog, M.D.

Loneliness, Social Isolation & Your Health

- 148 studies on the effects of social isolation on health found it is:
 - As bad as smoking 15 cigarettes a day.
 - As dangerous as being an alcoholic.
 - As harmful as never exercising.
 - Twice as dangerous as obesity.

Cacioppo JT, et al. *Ann N Y Acad Sci* 2011; 1231:17-22
Holt-Lunstad J, et al. *PLoS Med* 2010; 7:e1000316



Victoria Low Dog, M.D.

Meaning and Purpose

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

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

~ Mary Oliver

Vianna Low Dog, M.D.

One evening an old Cherokee told his grandson about a battle that goes on inside people

He said, "My son, the battle is between two "wolves" inside us all.

One is Evil.

It is anger, envy, jealousy, sorrow, regret, greed, arrogance, self-pity, guilt, resentment, inferiority, lies, false pride, superiority, and ego.

The other is Good.

It is joy, peace, love, hope, serenity, humility, kindness, benevolence, empathy, generosity, truth, compassion and faith."

The grandson thought about it for a minute and then asked his grandfather: "Which wolf wins?"

The old Cherokee simply replied,
"The one you feed."



Vianna Low Dog, M.D.