

## Integrative Medicine: *It's Not Alternative Anymore*



**Tieraona Low Dog, M.D.**

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

National Geographic's  
*Fortify Your Life*  
*Healthy At Home*  
*Life Is Your Best Medicine*

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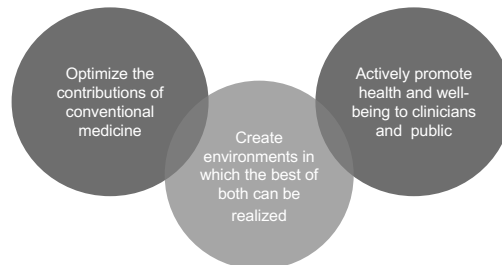
## *Healthcare in the United States*

- America spends **more per person** on healthcare than any other country—and does not have the best health outcomes.
  - \$9237 annually per capita spending
  - 1 in 3 adults are considered obese
  - 117 million people have at least one chronic disease
  - Life-expectancy rate is declining (78.8 years, compared to an average of 82.2 years among comparable countries)
- National **health spending is projected to grow** at an average rate of 5.6% per year for the next decade.

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## *Fostering Health and Well-Being*



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## *Imagine*

*Imagine a world, oriented toward healing rather than disease, where physicians believed in the natural healing capacity of human beings and emphasized prevention above treatment.*

*In such a world, doctors and patients would be partners working toward the same ends.*

Andrew Weil, MD



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## Integrative Medicine

**Integrative medicine and health reaffirms** the importance of the **relationship** between practitioner and patient, focuses on the **whole person**, is informed by **evidence**, and makes use of **all appropriate therapeutic and lifestyle approaches**, healthcare professionals and **disciplines** to achieve **optimal health and healing**.

Academic Consortium for Integrative Medicine & Health

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## Nutrition Matters

Nutrition problems single most important cause of death in the U.S.

- **Dietary factors**
- Tobacco smoking
- High blood pressure
- High BMI
- High plasma glucose
- Elevated cholesterol



JAMA 2018

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## Nutritional Guidance

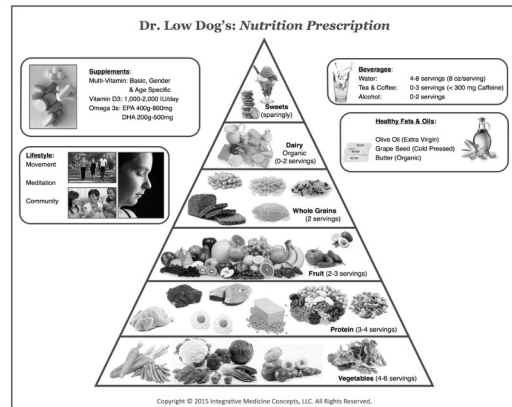


- Despite overwhelming evidence that **relatively small dietary changes** can significantly **improve health**, clinicians **seldom discuss nutrition** with patients.
- Poor nutritional intake and nutrition-related health conditions, such as **cardiovascular disease, diabetes, obesity, hypertension, and many cancers**, are highly prevalent in the United States, yet only **12% of office visits include any counseling about diet**.

Kahan S, et al. Nutrition Counseling in Clinical Practice: How Clinicians Can Do Better. *JAMA*. 2017;318(12):1101-1102.

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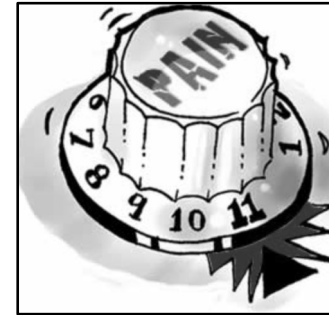
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## The Epidemic of Pain



- **>100 million Americans**—more than heart disease, cancer, diabetes combined.
- 50 million adults have **chronic pain**.
- 20 million report **severe pain**.
- 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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## Opiates

- Opioid industry more than \$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).
- In 2019, nearly **50,000 people** in the United States **died from opioid-involved overdoses**.
- 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 RL, et al. Drug Companies' Liability for the Opioid Epidemic *N Engl J Med* 2017; 377:2301-2305  
<https://links.nih.gov/show/tonics/opioids/chronic-overdose-epidemic>. Accessed April 25, 2022

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## Ibuprofen & Naproxen

- 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**.
- 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.  
Ruzchitska F, et al. *Eur Heart J* 2017 Nov 21;38(4):3282-3292.

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## Liver Toxicity



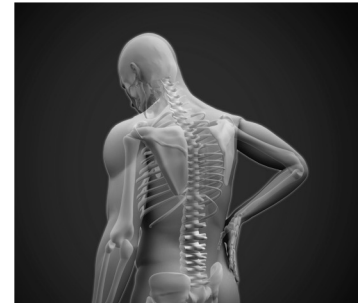
- Over past 40 years, **acetaminophen toxicity** accounts for **46% of all acute liver failure in the US** and **40–70% of all cases in Great Britain and Europe.**
- In 1975 *Lancet* editorial, “Surely it is time to **replace paracetamol** with an effective analogue which cannot cause liver damage.”

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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## 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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## 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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## 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-A83

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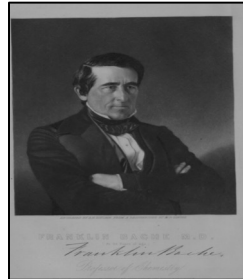
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## Acupuncture in the United States

- Dr. Franklin Baché, great grandson of Benjamin Franklin and founder of University of PA and first medical school in US, found acupuncture was highly effective for pain-management. In 1825 he translated French medical text on acupuncture into English.
- *Elements of Operative Surgery* (1829) contained a section describing acupuncture techniques.
- In 1836, Dr. William Markley Lee recommended acupuncture for pain relief in the *Southern Medical Journal* and the *Boston Medical and Surgical Journal* published an article on acupuncture for pain management.
- Fell into relative obscurity.



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

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## Nixon, China, and Acupuncture

- In 1972, James Reston, a *New York Times* reporter fell ill with appendicitis while covering President Nixon's trip to China.
- The surgeons in Beijing successfully used acupuncture as anesthesia during the reporter's surgery and after, to control post-operative pain. He was awake the whole time.
- Needles are not simply inserted into random points. Acupuncture is part of a 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 that **acupuncture is effective for the treatment of chronic musculoskeletal, headache, and osteoarthritis pain, and that treatment effects of 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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## Acupuncture & TMD



Small studies show **dry needling or acupuncture of the lateral pterygoid and posterior, periarticular connective tissue, masseter and temporalis muscles improves 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(3):225-232.

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## Acupuncture & Women's Health

- Data show acupuncture is beneficial for the treatment of **labor pain, back pain in pregnancy, and dysmenorrhea.**
- It is **unclear if it is effective** for *hyperemesis, chemotherapy-induced nausea and vomiting, and menopausal hot flashes*, though it might improve menopause related sleep disturbances.



Bishop KC, et al. Acupuncture in Obstetrics and Gynecology. *Obstet Gynecol Surv* 2019 Apr;74(4):241-251.

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SEARCH

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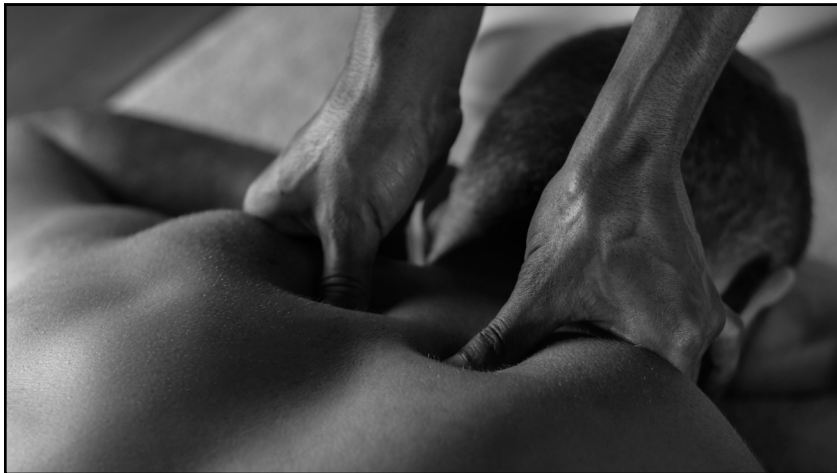
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FOR ACUPUNCTURE AND ORIENTAL MEDICINE

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[www.nccaom.org](http://www.nccaom.org)

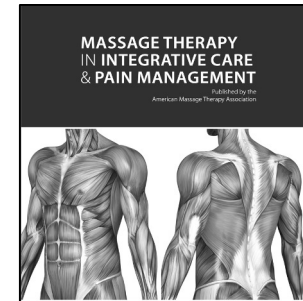
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## Massage Therapy

- Manual manipulation of soft tissue intended to promote health and well-being.
- Massage therapy is key component of pain management, overall health, and wellness.
- Incorporating into broader approach to pain management can help many suffering 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

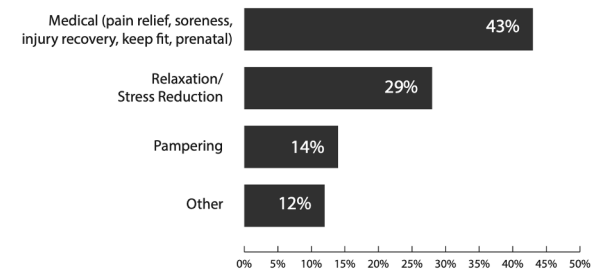
CHRONIC PAIN MANAGEMENT (pages 9-11)	BEHAVIORAL HEALTH TREATMENT (pages 12-13)	CARE FOR REHABILITATION/ PHYSICAL TRAINING (pages 13-16)	ACUTE MEDICAL TREATMENT (pages 16-20)
Back pain	Anxiety and stress	Performance training/ injury treatment	Cancer management
Neck and shoulder pain	Depression	Ergonomics 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](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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**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](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 and relaxing. Uses effleurage (long flowing strokes), petrissage (rolling, kneading), friction (deep, circular strokes), tapotement (tapping with cupped hand, hand edge). Relax.
- *Deep tissue*: slow deep strokes apply pressure to specific problem areas.
- *Sports*: variety of techniques to 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: Union of the Mind and Body*

- **Originated in northern India 5,000 years ago.**
- In general: yoga incorporates **breathing exercises, different postures, stretches, and meditation** to help one gain **greater acceptance, compassion, and centering.**
- **Many different types of yoga.**



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### *Some Types of Yoga*

- *Hatha*: umbrella term for all physical postures of yoga. Good for beginners, slower paced, focused on postures and breathing.
- *Iyengar*: focuses on alignment, poses held for long time while carefully adjusting pose. Good for those with injuries.
- *Vinyasa*: considered most athletic style, faster paced.
- *Ashtanga*: physically demanding sequence of poses. Advanced students.
- *Bikram/ Hot yoga*: 26 basic postures (each performed twice) in a room set to 105 degrees F and 40% humidity.
- *Prenatal*: adapted for pregnancy with pelvic floor and breath work, slow, uses props for support. Highly recommend.

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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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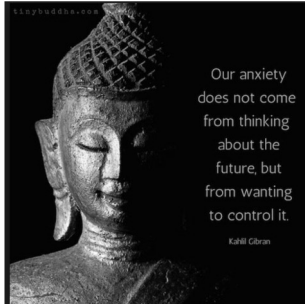


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## Meditation



- 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. *J-AMA Intern Med* 2014; 174(3):357-68

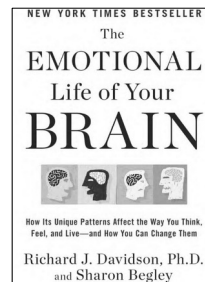
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## National Institutes of Health: The Evidence

- Mind-body therapies, such as meditation, have been shown to help relieve **anxiety, stress, fatigue**, and **general mood and sleep disturbances**, improving the **quality of life** of **cancer patients**.
- **Meditation may reduce blood pressure.**
- **Meditation-based programs may be helpful in reducing common menopausal symptoms.**
- **Meditation improves symptoms of anxiety.**

[www.nccih.nih.gov/health/tips/things-to-know-about-meditation-for-health](http://www.nccih.nih.gov/health/tips/things-to-know-about-meditation-for-health) Accessed April 4, 2022



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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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### Ginger (*Zingiber officinale*)



- Use dates back >5,000 years, cultivated India and China for spice and medicine. Important trade to Romans 2,000 years ago. By 14<sup>th</sup> century value 1 pound = to 1 sheep.
- Henry 8<sup>th</sup> passionate about ginger
- Queen Elizabeth 1st credited gingerbread man.
- Used fresh, dried, pickled, preserved, crystallized, candied, and ground. Actives increase with age in rhizome—9 months for greater spice, 5 months milder flavor.
- Contains many bioactive components, including gingerols, pungent active.

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### Nausea & Vomiting of Pregnancy

- Nausea and vomiting affects up to 85% of women during pregnancy.
- Studies done in *more severe* hyperemesis gravidarum.
- Meta-analyses: **ginger more effective than placebo** for hyperemesis gravidarum.
- Ginger **did not pose a risk for side-effects or adverse events** during pregnancy at doses of **250 mg dried ginger 4 times per day** (or 500 mg twice daily). *Do not exceed 1,500 mg per day.*



McParlin C et al. *JAMA* 2016; 316(13):1392-1401  
O'Donnell A, et al. *Health Technol Assess* 2016; 20(74):1-268

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**ACOG PRACTICE BULLETIN**  
Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 189, JANUARY 2018 (Replaces Practice Bulletin 153, September 2015)  
Committee on Obstetric Practice—This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics in collaboration with Susan M. Ramin, MD.

**First Line Therapy:**  
**Nonpharmacologic Options**  
Convert prenatal to folic acid supplement only  
→ **Ginger capsules 250 mg four times daily**  
Consider P6 acupressure with wrist bands

↓ persistent symptoms

**Pharmacologic Options**  
**Vitamin B6 (pyridoxine) 10-25 mg orally** (either taken alone or in combination with doxylamine 12.5 mg orally), 3–4 times per day. Adjust schedule and dose according to severity of patient's symptoms.  
**OR**  
Vitamin B6 (pyridoxine) 10 mg/doxylamine 10 mg combination product, two tablets orally at bedtime initially up to four tablets per day (one tablet in morning, one tablet in midafternoon and 2 tablets at bedtime).

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**Peppermint Essential Oil** (*Mentha x piperita*)

- High in menthol
- Documented **anti-inflammatory, analgesic, antimicrobial, antiseptic, astringent, carminative, fungicidal effects, nervine stimulant, decongestant, antispasmodic**
- Antispasmodic: **painful menstruation and IBS**
- **Relieves itching:** herpes, ringworm, scabies, poison oak, and ivy
- **Decongestant:** nasal congestion, cough




<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4606594/>

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**Peppermint Leaf** (*Mentha piperita*)

- **Meta-analysis RCTs:** soluble fiber, antispasmodic drugs, peppermint oil, and gut-brain neuromodulators for IBS. Most of low risk of bias.
- **Peppermint essential oil ranked first for efficacy when global symptoms** used as outcome measure, and **tricyclic antidepressants** ranked first for efficacy when **abdominal pain** 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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## Green Tea (*Camellia sinensis*)

- Systematic review: green tea reduces anxiety, benefits memory, attention and brain function (e.g., activation of working memory seen in functional MRI).
- Effects cannot be attributed to single constituent. Beneficial effects on cognition are observed under the combined influence of caffeine and l-theanine, whereas separate administration of either substance was found to have a lesser impact.



Mancini E, et al. Green tea effects on cognition, mood and human brain function: A systematic review. *Phytotherapy* 2017 Oct 15;34:26-37

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## *L-theanine: Natural Relaxant*

- Non-protein protein amino acid found in green tea. Animal models show neuroprotective and cognitive enhancing effects.
- Systematic review: 200–400 mg/d L-theanine can help reduce stress and anxiety in people exposed to stressful conditions.
- RDBPCT 30 healthy adults (~48 years old): 200 mg/d L-theanine showed beneficial effects on depression ( $p=0.019$ ), anxiety (0.006), sleep quality ( $p=0.013$ ); verbal fluency ( $p=0.001$ ) and executive function ( $p=0.031$ ), compared to placebo.

Williams JL, et al. *Plant Foods Hum Nutr* 2019; doi: 10.1007/s11130-019-00771-5.


Hidese S, et al. *Nutrients* 2019; doi: 10.3390/nu11102362.

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## Acute Respiratory Tract Infections

- **2017 systematic review** (33 RCT, N = 7,175) found **andrographis improved cough, sore throat and overall symptoms compared to placebo and other herbal treatments.**
- **12 studies meta-analysis** comparing andrographis to **usual care** (analgesics, antibiotics, anti-inflammatories, antivirals, corticosteroids, or steroids) indicated a **statistically significant reduction in sore throat and sick leave.**
- **AE ~10%, most common nonserious GI.**



Hu XY, et al. *PLoS One*. 2017;12(8): doi: [10.1371/journal.pone.0181780](https://doi.org/10.1371/journal.pone.0181780)  
 Worakunphanich W, et al. *Pharmacoevidentiol Drug Saf* 2021;30(6):727-739.

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## Probiotics



- **Live microorganisms** administered in adequate amounts confer *health benefit to the host.*
- Regulate/modulate immune functions, **reduce risk intestinal infection.**
- Improve **intestinal barrier functions, reduce endotoxemia.**
- Induce hypo-responsiveness to **food antigens.**
- Improve **glucose control** and **reduce inflammatory cytokines.**
- Inhibit tumorigenesis and **may inhibit cancer progression.**

Gianotti L, et al. *World J Gastroenterol*. 2010;16:167-175  
 Szulinska M, et al. *Nutrients* 2018, 10(6), 773; <https://doi.org/10.3390/nu10060773>

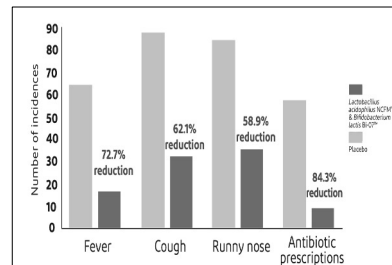
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## Prevention Cold and Flu-Like Symptoms

- **DBPCT 326 children** (3–5 years age) randomized to placebo (N = 104), *L. acidophilus* NCFM (N = 110), or *L. acidophilus* NCFM + *Bifidobacterium lactis* Bi-07 (N = 112). Children treated 2 x daily for 6 months.
- Both products superior to placebo but greater benefit seen for combination.

Leyer GJ, et al. Probiotic effects on cold and influenza-like symptom incidence and duration in children. *Pediatrics* 2009 Aug;124(2):e172-9.



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## Probiotics & Respiratory Infection



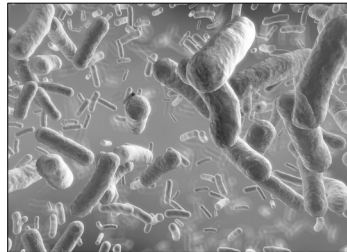
- **Meta-analysis 23 trials** (6269 children newborn—18 years) found probiotics reduced number of children having respiratory infections with fewer days absent from school.
- “Based on the available data and taking into account the safety profile of RCTs, probiotic consumption appears to be a feasible way to decrease the incidence of RTIs in children.”<sup>1</sup>

1. Wang Y, et al. *Medicine* 2016 Aug;95(31):e4509

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## Vaccine Adjuvant



Lei WT, et al. Effect of Probiotics and Prebiotics on Immune Response to Influenza Vaccination in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients*. 2017 Oct 27;9(11).

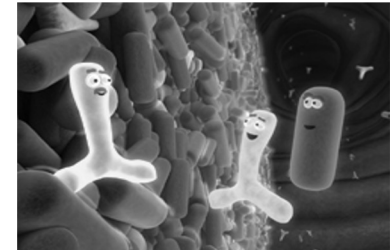
- 20 studies found “supplementation of influenza vaccines with **probiotics or prebiotics before vaccination** increased the immunogenicity to specific influenza viral strains, including the H1N1, H3N2, and B strains.”
- **Longer duration of pre-supplementation, the greater the response.** The older the adult, the more protection offered.
- Strains most active were *L. casei*, *L. paracasei*, and *B. longum*.

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## Acute Infectious Diarrhea

- High quality evidence support use in **acute infectious diarrhea (e.g., traveling, kids in daycare, etc.)**
  - Start first sign of diarrhea + 2 weeks beyond; start 2 days before travel + trip duration.
- Meta-analysis **17 RCTs** (2,102 children): significant **reduction in duration** of diarrhea *S. boulardii* (20 fewer hours).<sup>2</sup>
- Meta-analysis **8 RCTs** (1,229 children): *L. reuteri* reduced duration of diarrhea (25 fewer hours), increased cure rate on days 1 and 2.<sup>3</sup>



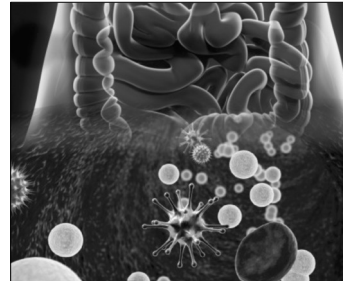
1. <https://www.sciencedirect.com/science/article/pii/S0950268817300101>, Accessed December 22, 2020
2. Feizadeh S, et al. Efficacy and safety of *Saccharomyces boulardii* for acute diarrhea. *Pediatrics*. 2014;134(1):e176-e191.
3. Urbanika M, et al. Systematic review with meta-analysis: *Lactobacillus reuteri* DSM 17938 for diarrhoeal diseases in children. *Aliment Pharmacol Ther*. 2016;43(10):1025-1034.

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## Proton Pump Inhibitors: GI Infection

- **PPIs disrupt microbiota.**
- Meta-analysis 23 studies (n=300,000): **65% increased risk *C. difficile*** associated diarrhea. (CDC lists *C. diff* “urgent threat”).<sup>1</sup>
- PPI users **5 times risk of developing GI infections** compared to non-users.<sup>2</sup>
- Significant association **between acid-suppressive therapies and risk of *C. difficile* and pneumonia in children.**<sup>3</sup>



1. Janarthanan S, et al. *Am J Gastroenterol* 2012;107:1001-10
2. Haffa RA, et al. *Ann Pharmacother*. 2018 Jul;52(7):613-622.
3. De Breyne P, et al. *Arch Dis Child* 2018; 103(1):78-82

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## PPI + Probiotics in Children



- 128 children with GERD randomized to **12 weeks PPI** (esomeprazole 1 mg/kg/d; max 40 mg) **plus probiotics** (*Lactobacillus reuteri* DM 17938) or identical **placebo**. Control: 120 healthy age-matched children.
- After 12 weeks, **dysbiosis occurred in 56.2% of group receiving placebo versus 6.2% of those taking probiotics (p<0.001).**
- **Probiotics + PPI significantly decreased prevalence of SIBO** among children with GERD compared to PPI and placebo ( $P < 0.001$ ).

Belei O, et al. *J Neurogastroenterol Motil*. 2018 Jan 30;24(1):51-57.

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## PPIs and the Immune System

- PPIs are risk factor for rotavirus, influenza, norovirus, and Middle East respiratory syndrome coronavirus infections; increased risk of acute gastroenteritis during periods of highest circulation of enteric viruses.<sup>1</sup>
- Review by Cedars-Sinai (53,130 people): once daily dosing conferred 215% increased risk positive COVID test, twice daily dosing 367% increased risk.
- Study in Korea found 79% greater risk of severe COVID if taking PPI.<sup>3</sup>

1. Charpiat B, et al. Proton Pump Inhibitors are Risk Factors for Viral Infections: Even for COVID-19? *Clin Drug Invest* 2020 Oct;40(10):897-899.  
 2. Almaraz CV, et al. Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors. *Am J Gastroenterol* 2020 Oct;115(10):1707-1715.  
 3. Lee SW, et al. Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching. *Gut* 2021 Jan;70(1):76-84.

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Outcome	Reference	No of studies/ participants	Evidence of benefit?	Prevention and treatment of Crohn's disease and ulcerative colitis	Satz-Laine et al (2013) <sup>11</sup>	14/821 ulcerative colitis 8/374 Crohn's disease	Yes
<i>Clostridium difficile</i> associated diarrhoea in adults and children	Goldenberg et al (2017) <sup>111</sup>	39/9955	Yes	←	Annanathan et al (2016) <sup>112</sup>	9/275	Yes
Necrotising enterocolitis	Al Faleh et al (2014) <sup>113</sup> Rees et al (2017) <sup>112</sup>	17/5338	Yes	←	←	13/805	Yes
Antibiotic associated diarrhoea in children	Goldenberg et al (2015) <sup>114</sup>	26/3898	Yes	←	←	7/425	Yes
Probiotics for preventing acute upper respiratory tract infections	Hao et al (2015) <sup>115</sup>	12/3720	Yes	←	Zhang et al (2016) <sup>116</sup>	6/1778	Yes
Urinary tract infections	Schwenger et al (2015) <sup>116</sup>	9/735	No	←	Ahalya-Jagoe et al (2016) <sup>117</sup>	19/935	Yes
Prevention of asthma and wheeze in infants	Azad et al (2013) <sup>117</sup>	6/1364	No	←	Mazidi et al (2017) <sup>118</sup>	11/641	Yes
Prevention of eczema in infants and children	Mansfield et al (2014)	16/2797	Yes	←	Hendjani et al (2017) <sup>119</sup>	15/976	Yes
Prevention of invasive fungal infections in preterm neonates	Agrawal et al (2015) <sup>120</sup>	19/4912	Unclear	←	←	6/1080	Yes
Prevention of nosocomial infections	Manzanarres et al (2015) <sup>121</sup>	30/2972	Yes	←	←	10/1656	Yes
Treatment of rotavirus diarrhoea in infants and children	Ahmadi et al (2015) <sup>122</sup>	14/1149	Yes	←	←		

From: Valdes AM, et al. Role of gut microbiota in nutrition and health. *BMJ* 2018;361:2179

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## Resource: [www.usprobioticguide.com](http://www.usprobioticguide.com)

Clinical Guide to Probiotic Products Available in USA Indications, Dosage Forms and Clinical Evidence to Date - 2019 Edition					
INDICATIONS FOR PEDIATRIC HEALTH					
Brand Name	Probiotic Strain	Dosage Form	CFU/dose	No of Doses/Day	Indications (Level of Evidence)
BioKult® Infant®	L. acidophilus 30™ L. rhamnosus P1008 56™ Bifidobacterium bifidum P1008 56™ L. acidophilus P1008 56™ L. rhamnosus 20™ L. acidophilus 20™ L. rhamnosus P1008 56™ L. acidophilus 20™	Sachet	100billion	1-1 sachet	GIAD - Childhood eczematous allergic dermatitis (I) C - Celiac (I) M - Infectious diarrhea - Adjusted to standard eradication therapy (I)
BioGaia® ProTectad® Baby Drops with Vitamin D3	L. reuteri DSM 17938	Drops	100billion	5 drops	AGD - Antibiotic associated diarrhea - Prevention (I) C - Celiac (I) GIAD - Childhood eczematous allergic dermatitis (I) CDI - Clostridium difficile disease - community acquired (I) C - Celiac (I) BSFAP - Infantile bowel syndrome/functional abdominal pain (I) D - Infectious diarrhea (I) Regurg GI Mot - Refluxes/regurgitation improves gastrointestinal motility (I)
BioGaia® ProTectad®	L. reuteri DSM 17938	Chewable Drops	100billion	1 sachet 5 drops	AGD - Antibiotic associated diarrhea - Prevention (I) C - Celiac (I) GIAD - Childhood eczematous allergic dermatitis (I) CDI - Clostridium difficile disease - community acquired (I) C - Celiac (I) BSFAP - Infantile bowel syndrome/functional abdominal pain (I) D - Infectious diarrhea (I) Regurg GI Mot - Refluxes/regurgitation improves gastrointestinal motility (I)
Dr. Merck® Good Start® Probiotic Powder Infant Formula	L. reuteri DSM 17938	Powder	100billion	1 sachet	AGD - Antibiotic associated diarrhea - Prevention (I) C - Celiac (I) D - Infectious diarrhea (I) Regurg GI Mot - Refluxes/regurgitation improves gastrointestinal motility (I)
Dr. Merck® Good Start® Probiotic Drops	L. reuteri DSM 17938	Drops	100billion	5 drops	AGD - Antibiotic associated diarrhea - Prevention (I) C - Celiac (I) GIAD - Childhood eczematous allergic dermatitis (I) CDI - Clostridium difficile disease - community acquired (I) C - Celiac (I) BSFAP - Infantile bowel syndrome/functional abdominal pain (I) D - Infectious diarrhea (I) Regurg GI Mot - Refluxes/regurgitation improves gastrointestinal motility (I)

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Patient: Doctor, I don't feel well and I'm not sure why.



Doctor: I want you to meditate for 20 minutes, twice a day, exercise for at least 30 minutes a day, avoid processed foods, eat plenty of organic fruit and veg, spend more time in nature and less indoors, stop worrying about things you can't control and ditch your T.V. Come back in 3 weeks.

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