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Gastroenterology 2019 Aug 27;

Peppermint Oil for Irritable Bowel Syndrome

A randomized trial shows no overall efficacy, although a small-intestinal–release formulation was helpful for certain symptoms.

Antispasmodics and peppermint oil are recommended and widely used for overall symptom improvement in patients with irritable bowel syndrome (IBS; *Am J Gastroenterol* 2018 Jun; 113 (suppl 2):1); however, the supporting evidence is sparse and derived from studies with methodological limitations.

In this multicenter, randomized, placebo-controlled trial, researchers assessed the efficacy and safety of two peppermint oil formulations in 190 patients meeting Rome IV IBS criteria (mean age, 34 years; 78% women; 96% Caucasian). Patients received identical-appearing capsules of 182 mg small-intestinal–release peppermint oil, 182 mg ileocolonic-release peppermint oil, or placebo for 8 weeks. The primary endpoints were abdominal pain response (per FDA definition: a $\geq 30\%$ decrease in the weekly average of worst daily abdominal pain compared with baseline in at least 50% of the treatment period) and overall relief of IBS symptoms (per European Medicines Agency definition: weekly relief score of 6 or 7 on a 7-point scale [7= complete relief] in at least 50% of the treatment period). Results were as follows:

- Abdominal pain response was not significantly different between groups (47% for small-intestinal–release peppermint oil, 41% for ileocolonic-release peppermint oil, and 34% for placebo).
- Overall symptom relief was also not significantly different (9.7%, 1.6%, and 4.7%, respectively).
- In secondary analyses, small-intestinal–release but not ileocolonic-release peppermint oil reduced abdominal pain, abdominal discomfort, and IBS severity compared with placebo.
- The most common side effects with small-intestinal–release peppermint oil were GERD symptoms and belching.

COMMENT: Peppermint oil did not meet the relatively stringent prespecified primary endpoints of this well-executed trial, although the authors point to a possible lack of statistical power. Peppermint oil, notably the small-intestinal–release form, can still be considered for patients with IBS whose dominant symptoms are abdominal pain and discomfort and who prefer an over-the-counter option with a more “natural” active ingredient.

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

CITATION(S): Weerts ZZRM et al. Efficacy and safety of peppermint oil in a randomized double-blind trial of patients with irritable bowel syndrome. *Gastroenterology* 2019 Aug 27; [e-pub]. (<https://doi.org/10.1053/j.gastro.2019.08.026>)

JAMA Intern Med 2019 Sep 3

More Evidence That Soft Drink Consumption Is Associated with Mortality

Associations were found for both sugar-sweetened and artificially sweetened drinks.

Soft drink consumption has been associated not only with weight gain and obesity but also with excess mortality in U.S. studies. In this prospective cohort study from 10 European countries, ≈450,000 participants (mean age, 51) completed questionnaires on dietary and clinical risk factors, including consumption of sugar-sweetened and artificially sweetened soft drinks. Participants with known heart disease, cancer, or diabetes were excluded. Mean follow-up was 16 years.

In adjusted analyses, mortality (mostly from cancer and cardiovascular causes) was 17% higher for participants who consumed 2 or more glasses of soft drinks daily compared with those who consumed less than 1 glass monthly. The mortality association was slightly stronger for artificially sweetened soft drinks than for sugar-sweetened soft drinks. Results were similar in participants whose body-mass index (BMI) was <25 kg/m².

COMMENT: These results have potential public health implications. The fact that excess all-cause mortality was associated with both sugar-sweetened and artificially sweetened soft drinks, regardless of BMI, deserves closer examination for possible mechanisms that might not involve weight gain. However, this observational study does not prove that the association is causal, and other unmeasured dietary and lifestyle factors might have influenced the results.

CITATION(S): Mullee A et al. Association between soft drink consumption and mortality in 10 European countries. *JAMA Intern Med* 2019 Sep 3; [e-pub]. (<https://doi.org/10.1001/jamainternmed.2019.2478>)

Estrogen-Only Systemic HT in the Setting of Bilateral Salpingo-Oophorectomy — Safe or Risky?

The answer is multifaceted: Outcomes of HT varied by women's age and BSO status.

To clarify the health effects of estrogen-only systemic hormone therapy (HT) in postmenopausal women without a uterus who did or did not undergo bilateral salpingo-oophorectomy (BSO), Women's Health Initiative researchers conducted an 18-year follow-up study involving 9939 women (age range, 50–79) who had been randomized to conjugated equine estrogen (CEE; 0.625 mg daily) or placebo for a median 7.2 years. Endpoints included coronary heart disease, invasive breast cancer, all-cause mortality, and a composite of serious health events (stroke, pulmonary embolism, colorectal cancer, and hip fracture).

Among women aged 50 to 69 without a uterus, systemic estrogen-only HT compared with placebo did not significantly raise risk for serious health events during treatment or long-term follow-up. Among younger women (age range, 50–59) who underwent BSO at hysterectomy, estrogen treatment was associated with a significant decrease in all-cause mortality during long-term follow-up (hazard ratio, 0.68; 95% confidence interval, 0.48–0.96). This mortality reduction was not observed among younger estrogen-treated women with hysterectomy but no BSO (HR, 0.93; 95% CI, 0.71–1.20). Among women aged 70 to 79 with BSO, risk for serious health events was significantly increased during estrogen treatment (HR 1.42, 95% CI 1.09–1.86); this excess risk was no longer statistically significant in cumulative follow-up (HR, 1.12; 95% CI, 0.94–1.34).

COMMENT: These results show that, in postmenopausal women without a uterus, systemic estrogen-only HT appears to be safe for those aged 50 to 69, both during treatment and after stopping or tapering such treatment. Among the subset of those aged 50 to 59 with BSO at hysterectomy, estrogen-only HT appears to reduce all-cause mortality during long-term follow-up; hence, these women should consider the potential health benefits of estrogen therapy. However, in women who are 70 or older, great caution should be exercised when initiating systemic estrogen therapy. I have never begun systemic estrogen for such women — and in those who started this treatment earlier (e.g., near menopause onset) and continue to take it after age 70, I try to taper the estrogen dose with the goal of stopping therapy. Lastly, it's worth noting that vaginal estrogen therapy for genitourinary syndrome of menopause is safe for postmenopausal women at all ages (NEJM JW Womens Health Feb 2019 and Menopause 2019 Jun; 26:603).

Andrew M. Kaunitz, MD, is an author of this study and Editor-in-Chief of *NEJM Journal Watch Women's Health* but had no role in selecting or summarizing this article.

CITATION(S): Manson JE et al. Menopausal estrogen-alone therapy and health outcomes in women with and without bilateral oophorectomy: A randomized trial. *Ann Intern Med* 2019 Sep 10; [e-pub]. (<https://doi.org/10.7326/M19-0274>)

Lancet Diabetes Endocrinol 2019 Jul 25; S2213-8587(19)30189-5

Just How Effective and Safe Is Testosterone Therapy in Women?

Review and meta-analysis confirm efficacy for women with bothersome low sexual desire, but conclusions about long term safety can't yet be drawn.

Although some clinicians manage bothersome low sexual desire by administering testosterone (T), no formulation specifically for women is available in most countries, including the U.S. Thus, researchers conducted a systematic review and meta-analysis of randomized, controlled trials of T in women. The study focused transdermal patches releasing 300 µg T daily (resulting in blood T levels at the upper end of the premenopausal range) or nontransdermal formulations at

doses achieving blood T levels close to those attained with the patch. Of the 36 trials (8480 participants), most were 12 to 24 weeks in length and the longest duration was 2 years.

Compared with placebo (or a comparator such as menopausal estrogen with or without progestin), T significantly enhanced sexuality outcomes, including event frequency, desire, pleasure, arousal, orgasm, and self-image in postmenopausal women affected by bothersome low sexual desire. Although transdermal T did not alter serum lipid levels, oral T increased LDL-cholesterol while reducing total and HDL-cholesterol as well as triglycerides. Although T was associated with weight gain and increased reports of acne and hair growth, it did not appear to cause serious adverse events.

COMMENT: Although this report did not yield evidence that T negatively affects cardiovascular, breast, or endometrial outcomes, the short-term nature of the trials do not allow conclusions to be drawn about T's long-term safety. I agree in principal with the editorialist that this meta-analysis supports use of transdermal T for menopausal women with bothersome low sexual desire. However, until formulations and doses specific for women become available, I remain reluctant to prescribe T for this indication.

CITATION(S): Islam RM et al. Safety and efficacy of testosterone for women: A systematic review and meta-analysis of randomised controlled trial data. *Lancet Diabetes Endocrinol* 2019 Jul 25; S2213-8587(19)30189-5; [e-pub]. ([https://doi.org/10.1016/S2213-8587\(19\)30189-5](https://doi.org/10.1016/S2213-8587(19)30189-5))

Gastroenterology 2019 Sep 6

Colectomy for Acute Diverticulitis: Old Habits Die Hard

Rates of elective surgery have continued to increase, mostly in patients aged 65 to 79, even after publication of more-conservative guidelines.

Since 2006, guidelines have departed from the traditional practice of referring patients with recurrent uncomplicated diverticulitis for elective colectomy (*NEJM JW Gastroenterol* Oct 2006 and *Dis Colon Rectum*

2006; 49:939). The current recommendation is that the decision to pursue surgery should be individualized. However, the impact of the updated guidelines on incidence of partial colectomy after uncomplicated diverticulitis is unclear.

To compare trends in colectomy before and after 2006, investigators conducted a retrospective cohort study of more than 3 million patients (age, ≥ 20) in a large national database who were hospitalized for diverticulitis between 2000 and 2016. Of these, nearly 750,000 underwent partial colectomy; 57% of the surgeries were elective.

Changes in rates of colectomy per 100,000 patients were as follows:

- Elective surgery rates increased by 0.13 per year before 2006 and by 0.06 per year after 2006.
- The slower-paced but continued increase was driven mostly by elective surgeries in patients 65 to 79 years old, among whom the rate more than doubled, from 0.10 per year before 2006 to 0.22 per year after 2006.
- Elective surgery rates decreased from 0.09 to 0.01 per year in patients 20 to 49 years old and from 0.23 to 0.04 per year in those 50 to 64 years old; rates increased slightly from -0.04 to -0.01 per year in those ≥ 80 years old.
- Urgent surgery rates decreased in patients 20 to 49 years old, 50 to 64 years old, and ≥ 80 years old but remained stable in those 65 to 79 years old.

COMMENT: Although it is not possible to attribute these trends solely to guideline uptake, the authors list several epidemiologic observations and sensitivity analyses that support the robustness of the findings. The bottom line for

clinicians is that the decision to refer patients to surgery has to balance several factors, including frequency and severity of attacks, surgical risk based on age and comorbidity, and patient preference.

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

CITATION(S): Strassle PD et al. Rates of elective colectomy for diverticulitis continued to increase after 2006 guideline change. *Gastroenterology* 2019 Sep 6; [e-pub]. (<https://doi.org/10.1053/j.gastro.2019.08.045>)

Lancet Neurol 2019 Oct; 18:942

Midlife Blood Pressure and Brain Abnormalities Decades Later

In cognitively normal adults, hypertension in midlife was associated with later-life white-matter lesions of presumed ischemic origin.

Hypertension is a powerful risk factor for ischemic and hemorrhagic stroke. The effects of blood pressure (BP) values and trajectories in midlife on subsequent brain morphologic changes are less clear, as is the effect of midlife hypertension on later cognitive decline.

In this substudy of a long-running project from the United Kingdom, investigators evaluated volunteers born in 1946 at ages 36, 43, 53, 60 to 64, and 69 years. Between ages 69 and 71, participants free of dementia underwent brain MRI to assess white-matter hyperintensity volume (WMHV) and whole-brain and hippocampal volumes. Participants also underwent amyloid PET scanning and cognitive testing.

Of 465 participants (mean age, 71; 51% men) who completed imaging and cognitive testing, 18% were amyloid positive on PET imaging and 29% were carriers of the Apo E ϵ 4 allele. At age 69, mean BP was 132/73 mm Hg and 40% of participants were taking antihypertensive medication. Higher systolic or diastolic BP at age 53 years, and higher BP increases between ages 43 and 53, were associated with increases in later WMHV. For every 10 mm Hg increase in systolic BP at age 53, subsequent WMHV increased by 7%; for comparable increases in diastolic BP, WMHV increased by 15%. The greater the increase in BP between ages 36 and 43, the smaller the hippocampal volume at ages 69 to 71 years. Absolute BP values or BP changes were not linked with amyloid positivity or overall cognitive scores.

COMMENT: These investigators are to be commended for assessing study participants at regular intervals and then correlating these assessments with a multifaceted brain-imaging protocol. The findings reinforce that midlife BP elevations are linked with increased risk for white-matter lesions of presumed ischemic origin. The lack of effect of BP elevation on amyloid suggests that small-vessel disease, not amyloid deposition, is a key mechanism by which hypertension harms the brain. BP screening and control in early adulthood could have important benefits.

CITATION(S): Lane CA et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): An epidemiological study. *Lancet Neurol* 2019 Oct; 18:942. ([https://doi.org/10.1016/S1474-4422\(19\)30228-5](https://doi.org/10.1016/S1474-4422(19)30228-5))

Running Water Therapy for Pediatric Burns

Treatment with cool running water was associated with improved outcomes, especially when administered for at least 20 minutes.

Recent evidence suggests that burns in adults heal better when treated with cool running water ([Burns 2019; 45:433](#); [PLoS One 2016; 11:e0147259](#)). To assess the effect of this treatment for pediatric burns, researchers queried an Australian burn center database that included structured interviews with patients and parents about first aid provided within 3 hours of injury, prior to burn center assessment. Running water therapy was classified as ≥ 20 minutes or < 20 minutes (which included none). Patients with friction, electrical, and chemical burns as well as those with missing data were excluded.

The analysis included 2495 children aged 0 to 16 years (median age, 2 years), of whom 90% suffered burns of $< 5\%$ body surface area. Overall, 71% of patients received ≥ 20 minutes and 29% received < 20 minutes or no cool running water therapy. Skin grafting, the primary outcome, was required in 7.8% of patients with ≥ 20 minutes of therapy versus 13.6% of those with < 20 minutes. Patients with ≥ 20 minutes also had significantly lower rates of hospitalization (13.2% vs. 18.0%) and full thickness burns (2.7% vs. 7.6%), but time to re-epithelialization did not differ between the two groups. The odds of skin grafting were significantly reduced with any duration of running water therapy (odds ratio, 0.6), with a dose-response relationship showing the greatest benefit in patients with ≥ 20 minutes.

COMMENT: Although observational, this study provides fairly convincing evidence that treatment of pediatric burns with cool running water as soon as possible improves important clinical outcomes. The authors note that durations longer than 20 minutes have not been shown to provide additive benefit and could be harmful, although that was not tested in this study.

CITATION(S): Griffin BR et al. Cool running water first aid decreases skin grafting requirements in pediatric burns: A cohort study of two thousand four hundred ninety-five children. *Ann Emerg Med* 2019 Aug 29; S0196-0644(19)30538-4; [e-pub]. (<https://doi.org/10.1016/j.annemergmed.2019.06.028>)

JAMA Pediatr 2019 Sep 9;

Taking the Good with the Bad: Positive Childhood Experiences Might Moderate Effects of Early Adversity

Positive childhood experiences predicted better mental health and social/emotional support in adulthood regardless of the number of adverse childhood experiences.

Research into the effect of early life experiences on later health has focused heavily on adverse childhood experiences (ACEs), yet positive childhood experiences (PCEs) are likely to play an important role in adult health outcomes.

Researchers evaluated behavioral risk factor data from a 2015 statewide survey of adults in Wisconsin. A 7-item PCE composite score was created using self-reported items related to feeling supported by and connected to family, friends, school, and the community as a child. Two adult outcomes — depression or poor mental health and reported social and emotional support — were analyzed by presence and level of PCEs. The relationships of PCEs to adult outcomes were stratified by level of ACEs. Adjustments were made for age, race/ethnicity, and income.

More PCEs predicted significantly lower odds of adult depression or poor mental health in a dose-responsive relationship (adjusted odds ratio, 0.3 for 6–7 vs. 0–2 PCEs; aOR, 0.5 for 3–5 vs. 0–2 PCEs) and significantly higher odds of reporting

“always” having social and emotional support as an adult (aOR, 3.5 for 6–7 vs. 0–2 PCEs). These relationships were similar across all ACE levels.

COMMENT: For years, we have focused primarily on how the bad things children experience lead to problems, but this study's findings reinforce our hope that even in the face of adversity, supportive relationships and connectedness create resilience. Clinicians should consider assessing the specific items in this study's PCE score in their conversations with older children and teens, as well as advising children and families on the cultivation and maintenance of such connections.

CITATION(S): Bethell C et al. Positive childhood experiences and adult mental and relational health in a statewide sample: Associations across adverse childhood experiences levels. *JAMA Pediatr* 2019 Sep 9; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2019.3007>)

Pediatrics 2019 Sep 9; e20190824

The Impact of Food Insecurity on the Development of Preschool-Age Children

Primary care pediatricians should be screening for food insecurity.

Access to nutritious food in early childhood (ages 0–4 years) is vital for normal development and school achievement. Food insecurity during these years has been linked to a range of health problems, from growth stunting to obesity as well as underweight.

To better understand the risks of food insecurity, researchers at medical centers in five U.S. cities used validated questionnaires to survey over 28,000 pairs of children and caregivers about food insecurity and children's growth, overall health, and developmental status. All children were aged <48 months. Food insecurity during the past year was assessed at both the household level and the child level (more severe).

The sample was ethnically diverse (50% non-Hispanic African-American and 34% Hispanic). The prevalence of food insecurity was 27% at the household level and 13% at the child level. Neither household food insecurity nor child food insecurity was associated with the child being obese, underweight, or stunted in growth. However, each type of food insecurity was associated with greater likelihoods of children having caregiver-reported fair or poor health and developmental risk.

COMMENT: In this large study, poor health and poor development, but not obesity, were associated with food insecurity. Addressing food insecurity in the children we care for and their households should be a high priority. Therefore, primary care offices should use screening questions to assess patients for food insecurity and make sure that families who screen positive are enrolled in available food assistance and nutritional programs. At programmatic and policy levels, pediatricians might work with food banks or assist in developing new strategies to overcome food insecurity, which are vitally needed.

CITATION(S): Drennen CR et al. Food insecurity, health, and development in children under age four years. *Pediatrics* 2019 Sep 9; e20190824; [e-pub]. (<https://doi.org/10.1542/peds.2019-0824>)

Antibiotics Before Blood Cultures Decrease Sensitivity

This time, the data support the dogma.

For patients with severe sepsis or septic shock, early administration of antibiotics improves outcomes. At the same time, guidelines recommend deferring antibiotics until blood cultures are obtained, so that cultures can confirm the diagnosis and guide future antimicrobial selection. These authors used an elegant study design to determine the precise impact of antibiotics on blood culture sensitivity.

In seven different emergency departments, they enrolled 330 patients with severe manifestations of sepsis (systolic blood pressure <90 mm Hg or lactate >4 mmol/L), in whom blood cultures were obtained before antibiotics were given. They then collected a second set of blood cultures 30 to 240 minutes after the first antibiotic was administered. Median (interquartile range) time from antibiotics to second set of culture collection was 70 (50–110) minutes.

Cultures obtained before antibiotics were positive for a pathogen in 31% of participants. Cultures obtained after antibiotics were positive in only 19%, yielding a sensitivity of 53%, using the preantibiotic culture as the gold standard. Adding cultures collected from other sites increased sensitivity, but only to 68%. Cultures obtained after antibiotics also took longer, on average, to grow organisms.

COMMENT; These data support the dogma that a short delay in antibiotics is reasonable to obtain blood cultures; the Surviving Sepsis Campaign recommends <45 minutes. Quality improvement efforts should focus on minimizing the time to obtain cultures, and then immediately providing antibiotics.

CITATION(S): Cheng MP et al. Blood culture results before and after antimicrobial administration in patients with severe manifestations of sepsis: A diagnostic study. *Ann Intern Med* 2019 Sep 17; [e-pub]. (<https://doi.org/10.7326/M19-1696>)

Geer JH and Siegel MD. Antibiotics and the yield of blood cultures: Sequence matters. *Ann Intern Med* 2019 Sep 17; [e-pub]. (<https://doi.org/10.7326/M19-2489>)

Reproductive Coercion and Relationship Abuse in Teens: An Important Wake-Up Call

Up to 17% of female high school students reported having experienced either or both of these forms of abuse.

In adolescents, relationship abuse including reproductive coercion (pregnancy coercion, condom manipulation, and other contraceptive sabotage) may contribute to sexually transmitted infections (STIs), unintended pregnancy, depression, substance abuse, and subsequent intimate partner violence. In a cross-sectional survey, investigators examined demographic differences, care-seeking, and sexual health behaviors among female students (age range, 14–19) seen at eight northern California school health centers who had experienced such abuse.

Of 550 students (40% Hispanic, 29% black, 16% multiracial, 13% Asian, 5% white) who had ever sex with a male partner, 12% reported reproductive coercion, 17% physical or sexual relationship abuse, and 17% nonpartner sexual violence during the previous 3 months, with no significant demographic differences. Likelihood of care-seeking did not differ for those who reported reproductive coercion only. In adjusted analysis, those experiencing relationship abuse were about twice as likely to seek STI testing or treatment. Students who reported both reproductive coercion and relationship

abuse were more likely to report having a partner ≥ 5 years older (adjusted odds ratio, 4.7), having ≥ 2 sexual partners, and using hormonal contraception without condoms (aOR, 3.8).

COMMENT: The marked prevalence of reproductive coercion and abuse seen among these high school students emphasizes the need to engage all adolescents in discussions that include inquiries about number and ages of sexual partners. The American College of Obstetricians and Gynecologists recommends periodic screening and offers guidance on harm reduction counseling (<https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Health-Care-for-Underserved-Women/Reproductive-and-Sexual-Coercion>).

CITATION(S): Hill AL et al. Reproductive coercion and relationship abuse among adolescents and young women seeking care at school health centers. *Obstet Gynecol* 2019 Aug; 134:351. (<https://doi.org/10.1097/AOG.0000000000003374>)

Mayo Clin Proc 2019 Aug; 94:1475

Spinal Stimulation for Chronic Pain

According to a meta-analysis of randomized trials, some patients derive substantial benefit.

For patients with intractable back or leg pain, implantation of a spinal cord stimulator is an option. This meta-analysis included 12 randomized trials (980 patients) of spinal stimulation (SS) during treatment durations of 6 to 12 months. Results were as follows:

- In three studies, SS was compared with medical therapy; these trials involved patients with diabetic neuropathy or failed back surgery and reported proportions of patients with $\geq 50\%$ pain relief. By this criterion, pain was relieved in half of SS patients and in 6% of medically treated patients — a significant difference.
- In three studies, researchers compared older and newer SS technology and used the $\geq 50\%$ pain relief criterion. Outcomes favored the newer devices, with response rates of about 70% (vs. $\approx 50\%$ with the older devices). These trials enrolled patients with chronic back and leg pain and complex regional pain syndromes.
- In three studies, older SS devices were compared with medical therapy, but average change in a numerical pain scale was reported as the main outcome. The mean difference was 1.4 on 0–10-point scales — a significant difference favoring SS. These trials enrolled patients with complex regional pain syndrome and peripheral vascular disease.
- Results were mixed in three other small studies of patients with failed back surgery.

COMMENT: Clearly, some properly selected patients derive substantial benefit from spinal stimulation. However, applying this analysis to individual patients is difficult, given the variety of pain syndromes and various types of stimulators included in clinical trials. Finally, note that most trials were funded by makers of SS devices, and risk for bias was considered to be “moderate.”

CITATION(S): Lamer TJ et al. Spinal stimulation for the treatment of intractable spine and limb pain: A systematic review of RCTs and meta-analysis. *Mayo Clin Proc* 2019 Aug; 94:1475. (<https://doi.org/10.1016/j.mayocp.2018.12.037>)
