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EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

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FPIN
Family Physicians Inquiries Network

FPIN envisions a primary care workforce that thinks critically, communicates expertly, and utilizes the best current evidence to improve the health of patients.

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EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

STATEMENT OF PURPOSE

Evidence-Based Practice (EBP) addresses important patient care questions asked by practicing family physicians, using the best sources of evidence in a brief, clinically useful format. Our goal is to instruct our authors on how to write peer-reviewed scholarly research for the medical and scientific community.

EDITORIAL POLICY

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DISCLOSURE

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Daily vitamin D supplementation to decrease recurrence of BPPV episodes? Let's pass on it

Jeong SH, Kim JS, Kim HJ, et al. Prevention of Benign Paroxysmal Positional Vertigo With Vitamin D Supplementation: A Randomized Trial. *Neurology*. 2020; 95(9): e1117-e1125. doi: 10.1212/WNL.0000000000010343

DOI 10.1097/EBP.0000000000001681

This investigator-initiated, blinded-outcome assessor, parallel, multicenter, randomized controlled trial in eight South Korean University dizziness clinics evaluated the effectiveness of vitamin D in preventing benign paroxysmal positional vertigo (BPPV) in 1,050 patients with recurrent vertigo. Data were collected over a four-year period. Enrolled patients were on average 62 years old with a confirmed history of recurrent BPPV episodes (most with posterior or horizontal type). All had similar quality of life (QOL) scores on the UCLA-Dizziness Questionnaire (UCLA-DQ) and no significant differences in bone mineral density screening laboratory examinations. Pregnant women, children, those with history of adverse reaction to vitamin D or calcium, and patients needing vitamin D or calcium supplementation for other reasons were excluded from this study. From the intervention group (n=500), researchers drew serum 25-hydroxyvitamin D, calcium, phosphorus, and parathyroid hormones at baseline, then at 2 and 12 months. Patients with vitamin D levels <20 ng/mL (n=348) were prescribed twice-daily oral 400 IU vitamin D plus 500 mg calcium carbonate for one year. The observation group did not have bone mineral density screening laboratory examinations drawn or receive placebo pills. All patients had access to treatment for active BPPV episodes. The primary outcome was a decrease in the patient annual BPPV recurrence rate (recurrence per 1 person-year), and secondary outcomes included the proportion of patients with recurrences, change in serum vitamin D levels, annual fall and fracture rates, and QOL defined by the UCLA-DQ. Prespecified adverse events included hypercalcemia and medication intolerance. The vitamin D and calcium intervention group had a lower rate of recurrence of BPPV than the observation group (0.83 recurrence/1 person-year vs 1.1 recurrence/1 person-year [incident rate ratio 0.76; 95% CI, 0.66–0.87]). This resulted in an absolute risk reduction of –0.27 (95% CI, –0.40 to –0.14; number needed to treat 3.7). Two patients in the intervention group withdrew because of hypercalcemia, and more patients withdrew for medication side effects in the intervention group compared with observation (5.8% vs 0.4%; number needed to harm=18). No significant difference was noted for annual fall and fracture rates and both groups noted improved QOL with UCLA-DQ scores over the study period. Limitations of this study included lack of placebo or blinding, and no vitamin D serologic testing in the control group.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	No	Implementable	Yes
Change in practice	Yes	Clinically meaningful	Yes

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching UpToDate and Dynamed with the terms [Benign Paroxysmal Positional Vertigo, Prevention, Calcium, Vitamin D] to find additional literature to place this research into the context of current clinical practice.

Bottom line: The study focused on a patient population diagnosed with recurrent BPPV who received vitamin D and calcium supplementation to decrease the recurrence rate of BPPV episodes, which is a patient-oriented outcome but may be an uncommon population. Patients with insufficient or deficient vitamin D levels did see a reduction in recurrence of BPPV episodes after supplementation. However, supplementation included calcium and we do not know the baseline vitamin D and calcium levels of the observation group, so knowing if low vitamin D levels lead to recurrent BPPV or if calcium supplementation was the reason for the improvement is difficult. Also, in the subanalysis, patients <65 years old did not see the same benefit with calcium and vitamin D supplementation as patients >65 years old.

Corey Lyon, MD
Melissa Beagle, MD, MPH
Roxanne Radi, MD, MPH
University of Colorado FMR, Denver, CO

The corresponding author is Corey Lyon;
COREY.LYON@ucdenver.edu.

The authors declare no conflicts of interest.

Consider oral fecal microbiota transplantation for your patients with recurrent *Clostridioides difficile*

Citation: Du C, Luo Y, Walsh S, Grinspan A. Oral fecal microbiota transplant capsules are safe and effective for recurrent *Clostridioides difficile* infection: a systematic review and meta-analysis. J Clin Gastroenterol. 2021;55(4): 300-308. doi:10.1097/MCG.0000000000001495

DOI 10.1097/EBP.0000000000001689

This systematic review with meta-analysis of 15 studies (12 case series and 3 randomized control trials) with 763 patients investigated the efficacy of oral fecal microbiota transplantation (FMT) capsules for the treatment of recurrent *Clostridioides difficile* infection (rCDI). Capsule administration of fecal microbiota was found to have an overall efficacy of 0.821 (95% CI, 0.72–0.784) in preventing recurrent infection after antibiotic failure. In the studies that compared oral administration with colonoscopic capsule delivery, no difference was observed in efficacy (relative risk 1.01; 95% CI, 0.95–1.08). No statistically significant difference was observed in efficacy between frozen and lyophilized capsules (0.82 vs 0.86, $P=.37$). No serious adverse events were directly attributed to the capsules, and the only hospitalizations during the follow-up period were related to treatment failure. The authors identified a low risk of publication bias among included studies; however, they noted that the evidence was overall deemed low-quality.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	No
Change in practice	Yes	Clinically meaningful	Yes

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here.

Bottom line: Heterogeneity of study protocols (concentration of fecal microbiota, the number of capsules used, and type of capsule preparation) and lack of accessibility for many primary care practices hinder general implementation of this intervention. Because oral FMT becomes more common in gastroenterology's management of rCDI, these protocols are likely to streamline and could very well be available in the not-so-distant future to primary care prescribers, especially for patients with contraindications to colonoscopy or fidaxomicin.

Roxanne Radi, MD MPH
Corey Lyon, DO FAAFP
The Denver Health Hospital Authority and The University of Colorado School of Medicine, Denver, CO

The corresponding author is Corey Lyon; corey.lyon@ucdenver.edu.

The authors declare no conflicts of interest.

Do hospitals that have implemented the WHO's "Baby-Friendly Hospital Initiative" achieve increased rates of exclusive breastfeeding at six months old?

EVIDENCE-BASED ANSWER

Infants born at "Baby-Friendly" hospitals are more likely to be exclusively breastfed at six months of life compared with usual care (SOR: **B**, meta-analysis of randomized controlled trials including single large randomized controlled trial). Birth at a "Baby-Friendly" hospital with high monitored compliance is associated with lower likelihood of breastfeeding cessation (SOR: **B**, cross-sectional study).

DOI 10.1097/EBP.0000000000001691

The Baby-Friendly Hospital Initiative (BFHI) is a 10-step evidence-based global program by the World Health Organization and United Nations Children's Fund to encourage successful breastfeeding through healthcare system policies, provider education, and patient support. At this time, over 20,000 maternity facilities in 150 countries have earned "Baby-Friendly" designation. Infants are considered exclusively breastfed (EBF) for three or six months if parents reported giving no solids, nonbreast milk, water, or liquids other than vitamins or medications.

A 2018 systematic review and meta-analysis of 27 randomized controlled trials (RCTs; N=36,051) examined the effectiveness of different breastfeeding support interventions on the rate of EBF at six months.[1] Patients were from the United States, Europe, Asia, Australia, and Africa, gave birth in a variety of settings, and received a variety of prenatal and postnatal inventions conducted by health professionals or laypeople including the BFHI, breastfeeding emotional support and counseling, breastfeeding education, or combined interventions. Comparison groups received the local standard of care (not specified). Data were analyzed in subgroup analyses of intervention type, intervention timing (prenatal only vs prenatal and postnatal vs postnatal only), intervention provider type (health professionals vs peers), use of predetermined provider training protocol or not, and intervention settings (hospital vs communities vs combined). In a subset of four studies, BFHI had a higher rate of EBF at six months compared with standard care (4 RCTs, N=20,555; odds ratio [OR] 5.2; 95% CI, 2.2–12.6). The meta-analysis was limited by potential selection bias because many studies were excluded because of lack of data at six months after birth and lack of EBF-specific results. Level of provider engagement represents a potential confounding variable in the studies that evaluated BFHI and EBF.

A 2001 multicenter cluster-randomized trial compared breastfeeding duration and exclusivity in full-term singleton mother–infant pairs in Belarus.[2] This was the largest RCT included in the meta-analysis above (n=17,046). The experimental intervention was modeled on BFHI and control consisted of usual breastfeeding practices. The primary outcomes were breastfeeding duration and EBF at 3, 6, and 12 months, with complete follow-up available for 16,491 pairs (96.7%). Infants from BFHI sites were significantly more likely than control infants to be breastfed to any degree at 12 months (19.7% vs 11.4%; adjusted OR 0.47; 95% CI, 0.32–0.69) and were more likely to be EBF at three months (43.3% vs 6.4%; $P<.001$) and at six months (7.9% vs 0.6%; $P=.01$). No difference in EBF was noted at 12 months. Generalizability may be limited for U.S. patients.

A 2018 national cross-sectional study in Switzerland investigated the association of birth at a current, former, or never "Baby-Friendly" hospital on duration of breastfeeding within the first year of life (n=1,326, with response rate of 40%).[3] Hospitals assessed for compliance with BFHI practices through monitoring audits. Singleton births occurred in current (508), former (425), and never (393) designated "Baby-Friendly" hospitals. EBF at six months was only 3%. Median duration of any breastfeeding was 32.7 weeks in current "Baby-Friendly" hospitals, followed by 30.5 weeks in former and 28.3 weeks in never "Baby-Friendly" hospitals, although no statistically significant difference was noted among the groups. In current "Baby-Friendly" hospitals with a monitored high level of compliance with BFHI components, an association with EBF was noted (n=508; hazard ratio for cessation of breastfeeding 0.62; 95% CI,

0.42–0.91). Limitations of this study included selection bias and nonresponse bias, variability in available compliance monitoring data, and low rates of EBF. EBP

Elise Sherman, MD
Chase Pitchford, MD
Hosea Covington, MD
Krystal Foster, MD
University of Missouri-Columbia Family Medicine Residency Program, Columbia, MO

The corresponding author is Krystal Foster, MD; fosterkry@health.missouri.edu.
The authors declare no conflicts of interest.

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In patients with diagnoses of overweight or obesity, does a plant-based diet improve weight loss compared with a non–plant-based diet?

EVIDENCE-BASED ANSWER

Yes. Plant-based diets—specifically vegan, lacto-ovo-vegetarian, lacto-vegetarian, and whole food plant-based diet—improve weight loss for adults with diagnoses of overweight or obesity (SOR: **A**, systematic reviews with meta-analyses of randomized controlled trials [RCTs] and an additional RCT with consistent findings).

DOI 10.1097/EBP.0000000000001688

A 2016 systematic review and meta-analysis of 12 randomized controlled trials (RCTs; N=1,151) compared vegetarian and nonvegetarian diets for their effects on weight in adults.[1] The median intervention duration was 18 weeks (range 8–96 weeks). Four RCTs had only female patients, while eight RCTs included men ranging from 13% to 16% of patients. Six RCTs included patients specifically with diagnoses of obesity or overweight, five included patients with diabetes, one included patients diagnosed with rheumatoid arthritis, and one included "healthy omnivores." The mean baseline body mass index (BMI) ranged from 25 to 53 kg/m^2. The vegetarian diets included vegan diets where all animal products are excluded (8 RCTs) and lacto-ovo-vegetarian diets where dairy products and eggs are allowed (4 RCTs). Six of the eight vegan RCTs used low-fat recipes while one used high-carbohydrate ingredients. The nonvegetarian diets varied and included low-fat diet, "habitual diet," "diabetes diet," National Cholesterol Education Program diet, and other diets with specified carbohydrate, fat, and protein ratios.

Patients on the vegetarian diets lost more weight than those assigned to the nonvegetarian diet (weighted mean difference [WMD] –2.0 kg; 95% CI, −2.8 to −1.2 kg). In addition, the subgroup analysis of the vegetarian diet groups (compared with control) showed that those on the vegan diet seems to lose more weight (WMD −2.5 kg; 95% CI, −3.0 to −2.0 kg) than those on the lacto-ovo-vegetarian diet (WMD –1.5 kg; 95% CI, –3.4 to 0.47 kg), although no direct statistical comparison between those two groups was performed. A subgroup analysis including studies only of patients with the diagnoses of overweight or obesity was not performed. Overall study quality was assessed as low (7 RCTs) or high (5 RCTs) with heterogeneity ranging from small in the vegan dietary group trials (I^2=3%) to large in the lacto-ovo-vegetarian trials (I^2=84%). Neither dietary intolerances nor potential side effects were reported for study groups.

A 2014 systematic review and meta-analysis of two RCTs, a non-RCT, and a cluster randomized trial (N=453) compared the weight change of adults following lacto-vegetarian or vegan diets to untreated comparison groups.[2] The review included studies of adults following a vegetarian or vegan diet for at least four weeks and reported outcomes of body weight. Only one small trial (n=11) was also included in the preceding review; populations in this systematic review were not limited to those with diagnoses of overweight or obesity. The included trials used vegan, lacto-vegan, or low-fat vegan diets for the intervention groups with "no dietary change," "usual diet," or omnivorous diet as controls. Patients had diagnoses of rheumatoid arthritis in two trials and "excessive weight" or diabetes in the other two trials. Interventions lasted 12 to 24 weeks, although it is not clear when outcomes were measured for each trial. An intention-to-treat analysis showed a mean change in body weight of –3.4 kg (95% CI, –4.4 to –2.4 kg) with the "vegetarian" diets versus controls. Key limitations of this review included concerning variance in baseline characteristics of study participants in study arms, moderate heterogeneity, and the small number of trials and total participants included in the primary quantitative synthesis.

A 2017 RCT (n=65) examined the effect of implementing a whole food plant-based (WFPB) diet on the primary outcomes of weight loss and dyslipidemia over six months.[3] Patients were adults in New Zealand with a BMI ≥ 25 kg/m^2 and at least one of the following comorbid conditions: type 2 diabetes, ischemic heart

disease, hypertension, or hypercholesterolemia. Both the control group and the intervention group received standard care for their diagnoses. In addition, the intervention group participated in a community-based program meeting twice weekly for two hours for the first 12 weeks promoting a low-fat WFPB diet with vitamin B_{12} supplementation and without energy restriction. Greater weight loss was seen in the intervention group compared with the control at both three months (–7.5 kg; 95% CI, –9.5 to –5.5 kg) and six months (–10.6 kg; 95% CI, –13.5 to –7.7 kg). Potential side effects of note included one participant on the WFPB diet who experienced hypoglycemia in the first week that resolved with insulin adjustment and one other who underwent cholecystectomy for cholecystitis. This RCT was limited by low sample size, high dropout rates (about a quarter of patients in each group) at six months, and multiple common confounders regarding dietary trials (lack of blinding, Hawthorne effect, and accounting for other health behaviors), and most trial authors were trustees of the "Plant Based New Zealand Health Charitable Trust." EBP

Carrie Wirth, MD
Jose Mitjavila, MD, MBA
Sherif Amin, MD
Oluwatobiloba Adenuga, MD
Indiana University School of Medicine Arnett Family Medicine Residency, Lafayette, IN

The corresponding author is Carrie Wirth, MD; cwirth@iuhealth.org.
The authors declare no conflicts of interest.

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In overweight and obese patients, is there an intermittent fasting strategy which results in the greatest weight reduction?

EVIDENCE-BASED ANSWER

Although intermittent fasting can be effective in achieving weight loss, no evidence exist that a specific intermittent fasting strategy results in greater weight loss (SOR: **A**, systematic review of randomized controlled trials [RCTs] and 2 single RCTs). There may be an association between skipping breakfast and an increased risk in weight gain (SOR: **C**, systematic review of cohort and cross-sectional studies).

DOI 10.1097/EBP.0000000000001649

A 2021 systematic review of 18 randomized controlled trial (RCTs; N=1,125) evaluated how intermittent fasting affected body weight in adults.[1] A subanalysis of six trials (N=667) restricted enrollment to both overweight and obese subjects and three trials (N=186) restricted enrollment to obese individuals only. Intermittent fasting protocols varied from alternate-day fasting (complete abstinence from calories on alternate days), periodic fasting (consumption of less than 25% required calories on specific days), or time-restricted eating (complete abstinence from calories for a specific time each day). Comparison groups for all nine trials were a form of continuous energy restriction (reduced calorie intake, nontime restriction). The follow-up periods ranged from 3 to 12 months. After pooling of the nine trials, subgroup analysis demonstrated no significant difference in weight loss between types of intermittent fasting in overweight and obese individuals ($\chi^2=4.52$, $P=.10$).

A 2020 RCT (n=116) compared weight loss effectiveness for time-restricted eating and consistent meal timing over a 12-week period.[2] Patients were overweight and obese adults (BMI of 27–43 kg/m^2); those who were pregnant, had a diagnosis of cancer or diabetes, had previous weight loss surgery, or were unable to adhere to the time-restricted eating schedule were excluded. Patients were randomized to either restricted eating from 8 PM to 12 PM the following day (n=59) or consistent meal timing (n=57) that had three structured meals per day. No restrictions on calorie intake or activity level were present between the groups. At 12 weeks, no difference in weight loss was noted between the time-restricted group and the consistent timing group (mean difference [MD] –0.26 kg; 95% CI, –1.3 to 0.78 kg).

A 2017 RCT (n=100) studied the differences of alternate-day fasting compared with daily calorie restriction on weight loss in overweight or obese adults.[3] Patients were nonsmokers with a BMI between 25 and 39.9 kg/m^2 and without cardiovascular disease, diabetes, pregnancy, or perimenopause or irregular menstruation. Patients were enrolled and randomized on a 1:1:1 ratio to alternate-day fasting, daily calorie restriction, and a no-intervention control group. The active trial duration was one year, preceded by a baseline phase of one month. The active phase consisted of six months of weight loss and six months of weight maintenance. The alternate-day fasting group consumed 25% of baseline energy intake as lunch on fast days and 125% of baseline energy intake split between three meals on feast days. The daily calorie restriction group consumed 75% of baseline energy intake split between three meals every day. Control group was instructed to maintain weight throughout without changing eating habits or physical activity. A significant reduction in weight was noted for both the alternate-day fasting group (MD –6.0%; 95% CI, –8.5% to –3.6%) and the calorie-restricted group (MD –5.3%; 95% CI, –7.6% to –3.0%) compared with the control group at 12 months. No significant difference was noted between the alternate-day fasting and daily calorie restriction groups at 12 months (MD –0.7%; 95% CI, –3.1% to 1.6%).

A 2019 systematic review and meta-analysis of nine cohort studies and 36 cross-sectional studies (N=425,281) evaluated the association between skipping breakfast and body weight in both children and adults of all weight classes.[4] Patients who skipped breakfast ("sometimes ate" or "never ate") were compared with those who reported eating breakfast daily. The definition of overweight and obesity varied somewhat across studies, but all used accepted definitions from accredited organizations. Patients were followed for at least one year. Those who skipped breakfast were significantly more likely to be overweight or obese compared with those who ate breakfast daily in both the cohort groups (9 studies, N=77,958; odds ratio [OR] 1.4; 95% CI, 1.3–1.7) and cross-sectional groups (36 studies, N=347,323; OR 1.5; 95% CI, 1.4–1.6). EBP

Jason Lanham, MD, MA, FAAFP
Paige White, MD
Eda Chen, MD
Eisenhower Army Medical Center, Fort Gordon, GA

The corresponding author is Jason Lanham; jlanhammd@gmail.com.
The authors declare no conflicts of interest.

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Is intuitive eating an effective approach for eating disorders?

EVIDENCE-BASED ANSWER

Intuitive eating, an eating style aimed at creating a positive relationship with food, the body, and physical activity, is associated with lower rates of body dissatisfaction and unhealthy behaviors aimed at weight control. (SOR **B**, systematic review of cross-sectional studies, prospective cohort studies, and observational study).

DOI 10.1097/EBP.0000000000001654

A 2015 systematic review of 24 cross-sectional studies (N=424,407) investigated intuitive eating (IE) in relation to other eating attitudes and behaviors, body image, and emotional functioning in adult women.[1] The inclusion criteria were female participants ≥18 years old, measurement of IE, and evaluation of psychosocial correlates, and the exclusion criteria were studies which were not analyzed by sex. Eight of the 24 studies examined IE in relation to other eating attitudes and behaviors. They demonstrated that IE was inversely associated with disordered eating symptomatology, according to total scores on several different scoring models including the Eating Attitude Test-26 and 21-item IE Scale (IES-T) and correlated negatively with bulimia, food preoccupation binge eating behaviors, and dieting (**TABLE**). Limitations of this systemic review included only cross-sectional studies and 12 of 24 studies included the same author.

A 2019 prospective cohort study (n=1,491) was performed to determine long-term associations between IE and psychological health and eating disorders as determined by self-report instruments. The primary instrument used was the 21-item IES-T.[2] Participants were members of 20 public schools in Minnesota and, after inverse probability weighting, were equal in sex and appropriately diverse in both socioeconomic status and ethnicity. Participants were followed for 8 years from adolescence (mean 14.5 years) to young adulthood (mean 22.2 years) and assessed for depressive symptoms, poor self-esteem, body dissatisfaction, unhealthy, and extreme weight control behaviors (fasting, minimizing food intake, using extreme food substitution, skipping meals, taking diet pills, inducing vomiting, and use of laxatives or diuretics). At follow-up, increased IE from baseline was associated with improvement in all the above-mentioned symptoms. The strongest "protective associations'' were seen when observing IE scores of those with binge eating showing that scoring one point higher than the mean at baseline gave 74% lower odds of binge eating behaviors (95% CI, 60–82%), and scoring one point higher at follow-up gave a 71% lower odds of binge eating (95% CI, 60–79%). The limitations of this study are that two subscales, Eating for Physical Rather Than Emotional Reasons and the Reliance on Internal Hunger/Satiety Cues, were used to evaluate IE which may have led to low internal consistency. In addition, the cross-sectional design cannot prove any causal relationships between IE and improvements in symptoms.

TABLE. Correlation ranges between disordered eating and different intuitive eating scales (r)

	Intuitive eating	All Intuitive eating subscales	Unconditional Permission to Eat subscale	Eating for Physical Reasons subscale	Reliance on Hunger/ Satiety Cues subscale
Disordered eating (including restrained eating, bulimia, binge eating, and dieting)	–0.5 to –0.7[a]	–0.1 to –0.7[a]	–0.4 to –0.7[a]	–0.1 to –0.4[a]	–0.2 to –0.4[a]

[a] $P<.001$, r=0.1 weak, r=0.5 moderate, r=0.7 strong, r=0.9 very strong.

A 2021 prospective cohort study (n=1,270) sought to evaluate the protective role of IE on eating disorders over time by predicting the onset versus continued absence of seven core eating disorder symptoms at 8-month follow-up. Participants were English-speaking female 18 years old or older who were enrolled through social media. Logistic regressions were completed for all variables. IE was a protective predictor of symptom onset for objective binge eating (OR=0.43; 95% CI, 0.31–0.58), subjective binge eating (OR=0.30; 95% CI, 0.23–0.38), purging (OR=0.33; 95% CI, 0.21–0.53), driven exercise (OR=0.57; 95% CI 0.45–0.74), fasting (OR=0.53; 95% CI 0.40–0.69), over evaluation (OR=0.33; 95% CI, 0.23–0.47), and fear of weight gain (OR=0.44; 95% CI 0.31–0.62). Overall, IE had the strongest protective influence on subjective binge eating, purging, and driven exercise onset, and a one unit increase in IE scores was associated with a 70%, 67%, and 43% decrease in the odds of experiencing the onset of these symptoms, respectively. Limitations of the study included the homogenous sample of predominately Caucasian female participants reducing generalizability. EBP

Heidi Beery, MD
Melissa Snell, DO
Seemal Kumar, MD, MPH, MBA
Simran Waller, MD, MPH
Roseburg Family Medicine Residency Roseburg, OR

The corresponding author is Heidi Beery, MD; hbeery@umpquachc.org.
The authors declare no conflicts of interest.

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Is topical green tea extract an effective treatment of acne vulgaris?

EVIDENCE-BASED ANSWER

Probably. Topical green tea application is beneficial for the treatment of inflammatory acne without causing significant adverse effects (SOR: **A**, meta-analysis of randomized controlled trials). Topical green tea reduces total lesion count for mild-to-moderate acne vulgaris (SOR: C, pre-post clinical study).

DOI 10.1097/EBP.0000000000001669

A 2020 meta-analysis of five randomized controlled trials (RCTs; N=247) examined the effectiveness of topical green tea extract (GTE) for the treatment of acne vulgaris.[1] Patients were 14 to 27 years old with 40% male from Iraq, Egypt, and South Korea. Studies were included if patients had a diagnosis of acne vulgaris with a range of acne severity characterized as mild, moderate, or severe, as defined by examining clinicians, and used GTE as an intervention. The intervention arms received GTE dosages ranging from 2% green tea lotion twice daily (BID) to 3% green tea emulsion BID, whereas the control arms received 5% zinc sulfate solution or nothing. The study durations ranged from 4 to 8 weeks with various follow-ups. The primary outcome was acne lesion count. The acne lesions were subcategorized as either inflammatory or noninflammatory in nature. Use of GTE significantly reduced the number of inflammatory acne lesions (4 trials, N=221; mean difference [MD], –9.38; 95% CI, –14.13 to –4.63; I^2=99%), compared with controls. The difference was believed to be clinically meaningful. However, no significant difference was observed in number of noninflammatory acne lesions between the two groups (3 trials, N=132; MD, –21.65; 95% CI, –47.52 to 4.22, I^2=99%). Adverse effects of topical administration were minimal such as transient, mild irritation, or itching. The review was limited by RCTs with small sample sizes, short treatment duration of 4 to 8 weeks, and lack of a standardized GTE.

A 2009 pre-post clinical study (n=20) examined the efficacy of 2% green tea lotion for the treatment of mild-to-moderate acne vulgaris.[2] This study was not included in the 2020 meta-analysis above because the study used a non-RCT design and included total lesion count (TLC) of papules and pustules and severity index (SI) as outcome measures. Patients were 70% female and were 15 to 36 years old with a mean age of 25 years old with mild-to-moderate acne. Mild acne was defined as less than 10 papules/pustules, and moderate acne was defined as 10 to 20 papules/pustules. Patients in the intervention group received 2% green tea lotion that was prepared by combining 3% GTE (75 mL) and ethanol to act as a preservative (25 mL, 95% purity) and applied it BID for six weeks with follow-up every two weeks. No control group was present because of the study design. To determine efficacy on acne severity, TLC and SI were used as outcome measures. TLC was calculated as the total number of papules and pustules, while the SI was scaled with numbers (1, 2, or 3) correlating to TLC in order of increasing intensity. TLC <10 was given an SI of one, TLC 10 to 20 was given an SI of two, and TLC >20 was given an SI of three. The primary outcome was the change in the mean TLC and SI scores at the end of the treatment compared with baseline. A 58% decline was observed in the mean TLC (baseline, 24 vs week 6, 10; MD 14, 95% CI, 8.58–19.42) and a 39% decline in the mean SI (baseline, 2.1 vs week 6, 1.3; MD 0.8, 95% CI, 0.54–1.26). More than one in six (15%) of patients complained of minimal pruritis that developed on the first day of application and lasted for three days, and 10% reported a stinging sensation on the first day that lasted 24 hours. This study was limited by small sample size and possible threats to internal validity because of lack of control group. EBP

Abhijeet Joshi, MD
Rami Elmasry, MD, DC
Zachary Shipp, MD
Southern Illinois University Decatur Family Medicine Residency, Decatur, IL

The corresponding author is Zachary Shipp; zshipp34@siumed.edu.

The authors declare no conflicts of interest.

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What is the most effective dose and route of misoprostol for labor induction?

EVIDENCE-BASED ANSWER

Vaginal misoprostol 25 to 50 μg every 4 to 6 hours may be slightly more effective than a similar oral regimen for achieving a vaginal delivery within 24 hours, with no increased risk of cesarean delivery, in women at term. However, there may be a 30% lower risk of uterine hyperstimulation and abnormal fetal heart rate changes with oral administration (SOR: **B**, meta-analyses of low-quality randomized controlled trials [RCTs]). The optimum dose and frequency of oral misoprostol is unclear (SOR: **B**, meta-analyses of low-quality RCTs). When combined with Foley catheter placement, vaginal misoprostol leads to delivery four hours earlier compared with buccal misoprostol plus Foley catheter (SOR: **B**, RCT).

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A 2021 systematic review and meta-analysis of 61 randomized controlled trials (RCTs; N=20,026) assessed the relative effectiveness and safety of various low-dose oral misoprostol regimens (≤50 μg) for induction of labor (IOL).[1] A subset of 33 studies (N=6,110) assessed oral versus vaginal misoprostol while three studies (N=360) compared different dosing regimens for oral misoprostol. Patients were at or near term, with a viable fetus, both with and without ruptured membranes. Multiple trials were from India (13 RCTs, N=2,533), Canada (4 RCTs, N=831), the United States (3 RCTs, N=644), Thailand (4 RCTs, N=447), Nigeria (2 RCTs, N=290), Sudan (2 RCTs, N=180), and Zimbabwe (2 RCTs, N=180); one trial each was included from Brazil (n=200), Iran (n=120), Saudi Arabia (n=146), South Africa (n=240), Taiwan (n=207),

and the United Kingdom (n=245). In trials comparing oral versus vaginal misoprostol, the oral dose varied from 10 to 50 μg, given as a single dose or as frequently as every hour, although most studies used 50 μg every 3 to 6 hours (22 RCTs, N=4,250). The vaginal misoprostol was either 25 μg (16 RCTs, N=3,338) or 50 μg (17 RCTs, N=2,774), typically given every 4 to 6 hours (29 RCTs, N=5,477). The primary outcomes were vaginal delivery (VD) within 24 hours, cesarean delivery (CSD), and uterine hyperstimulation with fetal heart rate (FHR) changes. Secondary outcomes were uterine hyperstimulation without FHR changes and oxytocin augmentation. Compared with vaginal misoprostol, oral misoprostol had a decreased incidence of VD within 24 hours (16 RCTs, N=3,451; relative risk [RR] 0.81; 95% CI, 0.68–0.95), decreased risk of uterine hyperstimulation with FHR changes (25 RCTs, N=4,857; RR 0.69; 95% CI, 0.53–0.92), and decreased risk of uterine hyperstimulation without FHR changes (16 RCTs, N=3,212; RR 0.69; 95% CI, 0.49–0.99). An increased risk of oxytocin augmentation was observed with oral versus vaginal misoprostol (28 RCTs, N=5,416; RR 1.3; 95% CI, 1.2–1.4) but no difference in CSD rates (32 RCTs, N=5,914; RR 1.0; 95% CI, 0.86–1.2). In trials evaluating various dose regimens of oral misoprostol, one small study (n=64) compared 20 to 25 μg titrated hourly versus 50 μg dosed every four hours and found no appreciable differences in VD (RR 0.60, 95% CI, 0.31–1.2), CSD (RR 1.3; 95% CI, 0.77–2.2), uterine hyperstimulation without FHR change, or oxytocin augmentation (no patients were present with uterine hyperstimulation with FHR changes in either group). Similarly, oral misoprostol 20 μg titrated hourly versus 25 μg dosed every two hours did not change the rates of VD (2 RCTs, N=296; RR 0.97; 95% CI, 0.80–1.2) or risk of CSD (2 RCTs, N=296; RR 1.66; 95% CI, 0.63–4.3). The risks of uterine hyperstimulation without FHR changes and oxytocin augmentation were not significantly different, and no cases of uterine hyperstimulation were present with FHR changes in either group. The review was limited by the underlying quality of the evidence which was judged to be low to very low.

A 2021 RCT (n=215) assessed the time to delivery for vaginal versus buccal misoprostol (combined with Foley catheter) for IOL in women with term pregnancies.[2] The patients were cared for at a single tertiary care hospital in Newark, Delaware; the mean age was 28 years old, 48% were non-White, and 67% were nulliparous. The mean body mass index was 34.1 kg/m^2. The indications for IOL were mainly maternal disease in 41% (eg, hypertension, preeclampsia, diabetes mellitus, renal disease, history of venous thromboembolism, cardiac disease, or other chronic medical condition), post-term pregnancy in 17%, and fetal concerns in 8%. At randomization, the average Bishop score was 1 (range 0–13; lower scores indicating lower chance of successful IOL), and the mean cervical dilation was 1 cm. In addition to placement of a Foley catheter for up to 12 hours, patients received 25 μg of either vaginal or buccal misoprostol, dosed every three hours for up to six total doses within 24 hours. Successful delivery was quicker in patients given vaginal compared with buccal misoprostol (19.7 vs 24.1 hours, respectively, $P<.001$). For secondary outcomes, the time to VD was shorter for the vaginal versus buccal misoprostol groups (16.8 vs 23.2 hours, respectively, $P<.001$). More women in the vaginal compared with buccal misoprostol group delivered within 24 hours (65% vs 49%, respectively, number needed to treat=6; $P=.02$). No difference was observed in CSD rates between the vaginal and buccal misoprostol groups (19% vs 23%, $P=.6$). Overall, no significant differences were observed between the two groups regarding procedures during labor, indications for CSD, maternal complications, or fetal outcomes. This study was limited by lack of blinding to the intervention among the patients and the providers, as well as lack of information on the average number of doses of buccal and vaginal misoprostol. EBP

Eloi Hoopman, DO[1]
Anh-Chi Do, MD[2]
Heather Nichols, MD[3]
[1]*East Pierce FMR, Puyallup, WA*
[2]*Valley Family Medicine Residency, Renton, WA*
[3]*FMRI Boise, Boise, ID*

The corresponding author is Eloi Hoopman, DO; ehoopman@multicare.org.
The authors declare no conflicts of interest.

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For pregnant women, does increased probiotic intake decrease the incidence of gestational diabetes?

EVIDENCE-BASED ANSWER

No. Regular consumption of yogurt containing active cultures with probiotic strains does not seem to alter the incidence of gestational diabetes compared with standard care (SOR: **A**, systematic review of randomized controlled trials [RCTs] and single case-control study). Higher levels of probiotic consumption compared with lower levels may be associated with a lower insulin resistance and a lower probability of gestational diabetes, although the mechanism behind the association is unclear (SOR: **C**, single RCT and case-control study).

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A 2021 systematic review of three parallel-group and four cluster randomized controlled trial (RCTs; N=1,647) assessed the effects of probiotic supplementation used with or without pharmacologic interventions for prevention of gestational diabetes.[1] Women already with a current diagnosis of gestational diabetes (but not history of) and those with certain high (variable definition) body mass index (BMI) levels were excluded. Probiotic supplements in addition to standard care were started before 20 weeks' gestation in six trials and at 20 weeks in the seventh. All studies included probiotic capsule supplementation with or without dietary intervention with the most common supplements being *Lactobacillus rhamnosus* or *Lactobacillus bifidobacterium* taken most commonly from enrollment or early pregnancy through delivery. Primary outcomes included the rates of gestational diabetes and of hypertensive disorders of pregnancy measured in the third trimester. After pooling six trials (N=1,440), probiotic supplementation did not decrease the risk of gestational diabetes compared with placebo groups (relative risk [RR] 0.80; 95% CI, 0.54–1.2). Probiotic use was also not associated with any difference in any hypertensive disorders diagnosed between the probiotic and placebo groups (4 trials, N=955; RR 1.4; 95% CI, 0.96–2.0). Limitations included wide CIs and broad heterogeneity between the study designs.

A 2013 RCT (n=70) examined the effect of daily probiotic yogurt consumption during pregnancy on insulin resistance and serum insulin levels.[2] Patients were 18- to 30-year-old Iranian primigravida female patients with a singleton pregnancy. Mothers with a history of gestational diabetes or hypertension, hepatic, or renal disease were excluded. Both groups consumed a set daily amount of probiotic yogurt containing *Streptococcus thermophiles* and *Lactobacillus bulgaricus*, with the intervention group also consuming two additional strains of lactobacillus in their yogurt. The primary outcomes were insulin resistance (homeostatic model), fasting blood glucose levels, and serum insulin levels, at nine weeks. Although serum insulin levels and insulin resistance did not decrease a significant amount after the trial period, compared with the regular probiotic group, the extra probiotic group developed less of an increase in serum insulin levels (mean difference [MD] 5 vs 1.2 μIU/mL, P=.02) and their insulin resistance increased less (MD +0.7% vs –0.2%, P= .01). Fasting plasma glucose levels and blood pressures were not affected by yogurt consumption.

A 2019 case-control study (n=249) assessed probiotic yogurt consumption and the relationship to the development of gestational diabetes.[3] Participants were from China, at 24 to 28 weeks' gestation with a singleton pregnancy and had no history of gestational diabetes. The mothers were required to have attended clinic regularly and have a baseline 75 g two-hour glucose tolerance test. Recall of consumption of *Lactobacillus acidophilus* and *Bifidobacterium* yogurt was comprehensively recorded by trained interviewers using structured questionnaires in face-to-face sessions. Yogurt consumption was defined for both preconceptions as well as during the gestational period, as high or low consumption and during which trimester consumed. Yogurt intake more than once a week was considered high with less than once a week marked low. Cases and controls were matched based on age and preconception BMI levels. The intervention and control groups had similar diet and exercise habits. Probiotic yogurt intake before pregnancy was not associated with an increase in gestational diabetes compared with those not consuming yogurt (odds ratio [OR] 0.77; 95% CI, 0.40–1.5). Of the mothers who did consume probiotic yogurt, those who consumed higher levels had a significant smaller proportion diagnosed with gestational diabetes compared with those in the low-intake group (OR 0.29; 95% CI, 0.15–0.58). EBP

Daniel Whitcomb, DO
Edward Rylander, MD
In His Image Family Medicine Residency, Tulsa, OK

The corresponding author is Daniel Whitcomb; daniel.whitcomb.do@gmail.com.
The authors declare no conflicts of interest.

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Is vitamin D an effective treatment for adults with depression?

EVIDENCE-BASED ANSWER

For patients with depression and confirmed vitamin D deficiency, vitamin D supplementation improves depression symptoms. However, in patients with depression but without confirmed vitamin D deficiency, or in patients without depression, supplementation does not improve depressive symptoms (SOR: **A,** multiple meta-analyses of randomized controlled trials).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2018 systematic review of four randomized controlled trials (RCTs; N=948) compared depression scores in adult patients with clinically diagnosed unipolar major depression treated with vitamin D3 supplementation versus placebo, no treatment, or fluoxetine alone.[1] Two trials used patients with laboratory-confirmed vitamin D deficiency (undefined in the paper); the other two did not examine vitamin D levels. Three of these studies were double-blinded, and one was unblinded. The trials randomized patients to vitamin D3 treatment groups with dosages ranging from 50,000 IU per week PO to 150,000 to 300,000 IU IM single dose to 1,500 IU per week PO plus fluoxetine 20 mg PO daily. Patients in the control groups were given 20 mg fluoxetine PO daily, placebo or no treatment. Treatment durations ranged from 8 to 52 weeks. Patients were assessed by either the Beck Depression Inventory (BDI) score or Hamilton Depression Rating Scale (HAM-D) (see **TABLE 1**). Pooled results demonstrated a moderate effect size (ES), suggesting that vitamin D supplementation had clinical benefits in patients with syndromal depression (ES 0.58, 95% CI, 0.45–0.72; $I^{22}=0$). Some limitations of the paper included a small number of studies meeting inclusion criteria, possible placebo response in the two studies that did not use allocation concealment, and the one unblinded paper. In addition, half of the studies did not examine baseline vitamin D level to determine whether supplementation was only beneficial to patients with vitamin D deficiency.

A 2015 meta-analysis of nine RCTs (N=4,923) reviewed the effect of vitamin D supplementation in reducing depressive symptoms among adults with a mean age ranging from 21.75 to 75 years from the United States, Australia, Norway, and Iran diagnosed with depression or depressive symptoms because of a medical condition.[2] Only three studies included patients with baseline vitamin D levels below 50 nmol/L, and one paper did not measure baseline vitamin D levels. Interventions included vitamin D_3 (400–1,500 IU/d), high-dose vitamin D (5,000–7,142 IU/d), vitamin D plus calcium (2,857–5,714 IU/d), vitamin D (200 IU/d) plus calcium and antidepressants, and calcitriol (0.25 g BID). Treatment duration ranged from 5 days to 5 years. Seven depression scoring tools were used, including Positive and Negative Affect Schedule, BDI, Fibromyalgia Impact Questionnaire, General Health Questionnaire, WHO Well-Being Index, SF12, Burnam Scale, Geriatric Depression Scale (GDS), and the HAM-D (see **TABLE**). Overall, vitamin D supplementation did not improve depressive symptoms, including when subanalyzed by baseline vitamin D level, duration of therapy, and dose of vitamin D. The authors concluded that the paper did not support the evidence for the efficacy of vitamin D in the improvement of depression among adults. One limitation of the paper was that most of the included studies

TABLE. Outcome measures

Outcome measure	No. of items	Scoring scale	Interpretation
Beck Depression Inventory (BDI)	21	0–63	Higher scores indicate more severe depressive symptoms
Hamilton Depression Rating Scale (HAM-D)	17	0–52	Higher scores indicate more severe depressive symptoms
Profile of Mood State	65 or 35	Varies by scale	Higher scores are indicative of people with less stable mood profiles
Short Form Survey (SF12)	12	0–100	Measures 8 domains of physical and mental health. Higher scores indicate higher physical and mental health functioning
Questionnaires on premenstrual syndrome, fibromyalgia, and menopause	N/A	N/A	Components of questionnaires referring to depression were used from the Premenstrual Symptoms Rating, Fibromyalgia Impact Questionnaire, and Menopause Symptoms Questionnaire
Positive and Negative Affect Schedule	20	10–50	Measures positive and negative affect separately. Higher scores indicate increased positive affect
Fibromyalgia Impact Questionnaire	10	0–100	Measures impact of fibromyalgia on functioning. Higher scores represent a greater impact of fibromyalgia on the person
WHO Well-Being Index	5	Raw scores range from 0 to 25	Self-reported measure of current well-being. 0 represents worst possible, and 25 represents best possible quality of life
General Health Questionnaire	12	0–36	Identification and measurement of nonpsychotic psychiatric disorders. Higher scores indicate increased psychological problems and distress
Burnam Screen for Depression	20	0–60	Higher scores indicate more severe depressive symptoms
Geriatric Depression Scale (GDS)	30	0–30	Used to identify depression symptoms in elderly adults. Higher scores indicate more severe depressive symptoms

enrolled patients with low levels of depression and normal baseline vitamin D levels.

A 2014 systematic review and meta-analysis of seven RCTs (N=3,191) examined vitamin D supplementation for depressive symptoms in adults 18 to 79 years old with and without depressive symptoms from four diverse geographical locations.[3] Three of the seven RCTs required a low baseline vitamin D level (undefined) or documented deficiency (defined as <50 nmol/L). All seven trials used depressive symptom scaling scores (GDS, BDI, HAM-D, and Burnam scale), included supplementation with vitamin D3 (cholecalciferol) from 600 to 300,000 IU (dosing frequency daily to annually), and had a follow-up period of 6 weeks to 2 years. Overall, vitamin D supplementation showed no significant effect on depressive symptoms (standardized mean difference [SMD] –0.14, 95% CI, –0.33 to –0.05); however, subgroup analysis found a moderate improvement in patients with clinically significant depressive symptoms or depressive disorder (2 studies: SMD, –0.60; 95% CI, –1.19 to –0.01; P=.05). The authors noted that 5 of 7 RCTs had unclear or high risk of bias per Cochrane risk of bias scale. EBP

Marc Pascuzzo, PsyD
Nate Hainsworth, DO
Lisa Kingsley, DO
Austin Klomp, DO
Colleen Maher, DO
HealthONE Family Medicine Residency, Aurora, CO

The corresponding author is Marc Pascuzzo, PsyD; marc.pascuzzo@outlook.com.
The authors declare no conflicts of interest.

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Is there an ideal time of year to receive the flu vaccine?

EVIDENCE-BASED ANSWER

Influenza vaccine effectiveness wanes after administration with a 16% increase in the odds of infection for every additional 28 days after immunization (SOR: **B**, retrospective cohort study). The Centers for Disease Control and Prevention (CDC) recommends vaccination before seasonal community influenza activity begins, and by the end of October (SOR: **C**, practice guideline based on expert opinion).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A multiseason retrospective cohort study (N=44,959) encompassing seven seasons of data between 2010 and 2017 examined whether the risk of testing positive for influenza increased with time since vaccination.[1] Patients were two years old or older, in the Kaiser Permanente Northern California integrated healthcare delivery system, who underwent real-time reverse-transcriptase polymerase chain reaction (RT-PCR) testing 14 days or more from inactivated influenza vaccination. The mean age was 58 years, and all patients had received the influenza vaccine between September 1 and March 31. Patients who received more than one influenza vaccination during a season, received an RT-PCR test before vaccination, or received a live-attenuated vaccine were excluded. The primary outcome was RT-PCR confirmed cases of influenza and there were no secondary outcomes. However, respiratory syncytial virus (RSV) was used as a negative-control outcome to regulate for confounding factors (as RSV prevalence should not be affected by influenza vaccination or waning but is subject to similar risk factors and seasonal patterns as the influenza virus). The rate of influenza positivity increased linearly by 16% per 28 days since vaccination (odds ratio 1.2; 95% CI, 1.1–1.2). Odds of testing positive at 42 to 69 days after immunization was 1.3 (95% CI, 1.1–1.6), which increased to 2.1 (95% CI, 1.7–2.5) at 154 or more days after vaccination. This retrospective cohort study was limited by intraseasonal vaccine efficacy and variability in circulating viral strains, which caused unpredictable differences in overall vaccine effectiveness and waning from year to year. The study also did not account for geographic differences and population variability.

In 2021–2022, the Advisory Committee on Immunization Practices was chartered to provide expert external advice as a Federal Advisory Committee to the CDC. Their guidelines for the use of seasonal vaccines in the prevention and control of influenza were based on a systematic review and evaluation of updates as well as additions to applicable literature in the English language.[2] The guideline stated that optimal vaccination coverage should start before the appearance of influenza activity in the community (which cannot be determined in advance), and that early vaccination in July and August should be avoided in nonpregnant adults. The guideline also recommended offering vaccination by the end of October, after balancing considerations of unpredictable seasonal timing, waning immunity, and vaccine effectiveness (evidence from opinion of authorities and/or reports of expert committees). EBP

Courtney Getchell, MD
Holly Payne, MD
Daniel Lew, DO
Carl R. Darnall Army Medical Center Family Medicine Residency Program, Fort Hood, TX

The corresponding author is Daniel Lew, DO; daniel.b.lew.mil@health.mil.

The authors declare no conflicts of interest.

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Does peppermint essential oil relieve headache pain in adults with tension headaches?

EVIDENCE-BASED ANSWER

Topical peppermint oil may provide improvement of tension headache pain compared with placebo (SOR: **B**, 2 randomized control trials [RCTs]). Peppermint oil may improve pain associated with heat and ischemia (SOR **B**: 1 RCT).

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A 2016 report described two randomized control trials (RCTs) testing the effectiveness of topical peppermint oil with and without an oral analgesic to reduce headache pain.[1] A double-blinded RCT compared the effectiveness of topical peppermint oil or placebo with oral paracetamol or oral placebo both with traces of peppermint oil to allow for proper masking in reducing the intensity of headache pain. Adults (N=105) with episodic or chronic tension-type headaches and migraines received all four possible treatments in a randomized sequence. Treatments included oral medication (1,000 mg paracetamol or placebo) and a cutaneous application (5 mL peppermint oil or placebo). While at home, patients applied cutaneous substance to the forehead and temporal skin at headache onset and reapplied substance at 15 and 30 minutes and took the oral medication at the onset of headache. Headache intensity was self-reported in a diary from baseline up to four hours posttreatment on a five-point rating scale, from no headache (0) to severe (4). Four hours posttreatment, the percentage of patients who achieved clinical improvement (reduced ratings from 4, 3, or 2, to 1 or 0) was significantly lower in the placebo group (30.5%) compared with the peppermint oil group (56.2%, $P<.05$), the paracetamol group (54.3%, $P<.05$), and the combined treatment group (66.7%, $P<.05$). The study test products were well-tolerated.

The second double-blinded RCT in the same report compared the effectiveness of topical peppermint oil or placebo with oral acetylsalicylic acid or oral placebo in reducing the intensity of headache pain. Adults (n=44) with episodic or chronic tension-type headaches and migraines received all four possible treatments in a randomized sequence. Treatments included oral medication (1,000 mg acetylsalicylic acid or placebo) and a cutaneous application (5 mL peppermint oil or placebo). While at home, patients applied the cutaneous substance to the forehead and temporal skin at the onset of headache and reapplied it at 15 and 30 minutes. They also took oral medication at the onset of headache. Headache intensity was self-reported in a diary from baseline up to four hours posttreatment on a five-point rating scale, from no headache (0) to severe (4). Four hours posttreatment, the percentage of patients who achieved clinical improvement (reduction from 4, 3, or 2, to 1 or 0) was significantly lower in the placebo group (27.3%) compared with the peppermint oil group (77.3%, $P<.05$), the acetylsalicylic acid

group (86.4%, $P<.05$), and the combined treatment group (88.6%, $P<.05$). The study test products were well-tolerated.

In 1994, a double-blinded RCT crossover study investigated the effects of peppermint oil and eucalyptus oil preparations on self-reported pressure, ischemic, and thermal pain.[2] Healthy 20- to 30-year-old male participants (N=32), who had no headache at the time of the study or history of chronic headache, were included in the study. On each of four separate days, patients received 1) 10 g peppermint oil+5 g eucalyptus oil+ethanol 90% to 100 g, 2) 10 g peppermint oil+trace eucalyptus oil+ethanol 90% to 100 g, 3) trace peppermint oil+5 g eucalyptus oil+ethanol 90% to 100 g, or 4) placebo: trace peppermint oil+trace eucalyptus oil (aided in masking)+ethanol 90% to 100 g. Headaches were simulated with different modalities: pressure to head and pressure to finger, thermal application to forehead, and reduction in circulation to temporal vasculature via collar. Pain was assessed on a 0–50 point scale, inversely proportional to the time needed to induce pain. A higher score indicated greater pain sensitivity. Peppermint oil significantly reduced pain sensitivity for thermal ($P<.001$) and ischemic pain ($P<.01$), but not head or finger pressure induced pain. EBP

Namita Bhardwaj, MD, MS, MPH
Michael Chavez, MD
Jeremy Fleeks, MD
Alexander Ondari, MD
Shelby Payne, MD
University of Texas Medical Branch, Galveston, TX

The corresponding author is Namita Bhardwaj; nabhardw@UTMB.EDU.

The authors declare no conflicts of interest.

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In normotensive adults with diabetes, does adding an ARB or ACE-inhibitor reduce cardiovascular events?

EVIDENCE-BASED ANSWER

No. ACE-Is or ARBs do not reduce CV events in normotensive adults with diabetes within a five-year follow-up (SOR: **B**, 2 meta-analyses of randomized controlled trials with variable quality).

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A 2012 meta-analysis of 13 randomized controlled trials (RCTs; N=80,594) evaluated cardiovascular benefits of ACE-Is or ARBs in adults with, or at risk for, atherosclerosis.[1] The review included trials that were 12 or more months in duration and had ≥1,000 patients. Study participants' mean ages ranged from 55 to 67 years old, mean systolic blood pressures at baseline ranged from 126 to 152 mmHg, and most patients (79%) were taking non–ACE-I, non-ARB antihypertensive medication during the trial. Patients on concomitant renin-aldosterone-angiotensin system antagonists were excluded. Participants were stratified according to baseline blood pressure (systolic blood pressure <130, 130–139, and ≥140 mmHg). The review included a subgroup of 3,394 patients with diabetes mellitus type 1 (DM-1) or type 2 (DM-2). Patients were assigned to ACE-I or ARB (medication and dose varied) versus placebo. The primary outcome was a cardiovascular event composite of stroke, myocardial infarction, or cardiovascular death. Patients were followed up to five years. In overall normotensive adults (systolic BP <130 mmHg), regardless of diabetes status, ACE-Is or ARBs reduced CV events compared with placebo (13 studies, N=23,922; OR 0.83; 95% CI, 0.75–0.91; I^2=9%). However, in normotensive adults with DM-1 or DM-2, ACE-Is and ARBs did not reduce CV events when compared with placebo

(4 studies, N=3.394; OR 0.91; 95% CI, 0.76–1.09). The studies specifically looking at diabetic patients had high heterogeneity (I^2=70%), indicating large variability between them.

A 2020 meta-analysis of 13 RCTs (N=1,282), with no overlap with the meta-analysis above, looked at the effects of ACE-Is and ARBs on cardiovascular events, all-cause mortality, and adverse events, as well as improving renal outcomes in patients with diabetic kidney disease.[2] Mean patient ages ranged from 38 to 60 years old, predominant sex was male (67%–78%), and patients were followed for 1 to 6 years. All patients had diabetic kidney disease (defined as urinary albumin excretion >30 mg/d or estimated glomerular filtration rate<60 mL/min/1.73 m^2) and were "normotensive" (not defined by study authors). Participants received an ACE-I/ARB (medication and dose varied) versus placebo or nifedipine (10–40 mg bid). A subgroup within this meta-analysis examined cardiovascular outcomes (specific outcomes not defined). ACE-I/ARBs did not decrease cardiovascular events compared with placebo (3 studies, N=302, 8.7% [ACE-I/ARB] versus 13% [placebo]; RR 0.97; 95% CI, 0.45–2.1). Adverse events (including cough, hypotension, and hyperkalemia) were similar between intervention and placebo groups (8 studies, N=931, 7.4% vs 7.2% reported; OR 1.12; 95% CI 0.69–1.81). Limitations of this study included a lack of definition of normotension, heterogeneity of doses and types of ACE-Is and ARBs, and small study populations. EBP

Madeleine Davies, PharmD
Tera Meerkins, PhD
Dana Brandenburg, PsyD, LP
Carrie Link, MD
University of Minnesota Medical Center Residency Program, Minneapolis, MN

The corresponding author is Dana Brandenburg, brand444@umn.edu
The authors declare no conflicts of interest.

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Does cognitive behavioral therapy without pharmacotherapy improve eating disorder remission rates?

EVIDENCE-BASED ANSWER

Cognitive behavioral therapy (CBT) improves long-term remission rates in patients with various eating disorders, including binge-eating disorder, anorexia nervosa, and bulimia nervosa (SOR: **B**, a meta-analysis of randomized controlled trials [RCTs] and observational study). In patients with binge-eating disorder, CBT-based psychotherapy reduces binge-eating episodes and body mass index for up to 12 months (SOR: **B**, a meta-analysis of RCTs, non-RCT, and non-controlled trials). CBT abstinence rates for binge-eating disorder are generally higher than other eating disorder types (SOR: **B**, meta-analysis of non-RCTs).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 meta-analysis of 62 articles (N=4,368) studied the treatment effects of cognitive behavioral therapy (CBT) and psychodynamic-interpersonal therapies (PITs) for eating disorders .[1] The meta-analysis included randomized controlled trials (RCTs) and observational studies of outpatients diagnosed with eating disorders who underwent at least one psychotherapeutic intervention that had a cognitive behavioral or psychodynamic focus, outcomes of efficacy or treatment effectiveness, and data available to

calculate event rate for eating disorder remission. Interventions other than CBT or PIT and duplicated trials were excluded. The eating disorders included anorexia nervosa, bulimia nervosa, and binge-eating disorder. Eating disorder remission was defined variously: weight normalization in anorexia, cessation of compensatory behaviors in anorexia and bulimia, and cessation of binging in bulimia nervosa and binge-eating disorder. Rather than numbers of subjects for each intervention and diagnosis, the authors reported numbers of samples (k). CBT for binge-eating disorder had a higher event rate for remission than other diagnostic groups; however, all groups achieved significant remission rates with CBT. Remission rates for each diagnosis were 50% for binge-eating disorder (95% CI, 42–57; k=15), 33% for anorexia (95% CI, 28–40; k=17), 28% for bulimia (95% CI, 22–34; k=15), and 30% for mixed samples (95% CI, 25–35; k=19). The limitations of this study were the inclusion of observational studies and not accounting for the baseline comorbid psychology disease severity.

A 2020 meta-analysis of 114 articles (n=8,862) studied the long-term effectiveness of psychotherapy and medical treatment of binge-eating disorder and weight loss.[2] English-written RCTs, non-RCT, or uncontrolled trials regarding the psychological and medical treatment of binge-eating disorder diagnosed using *DSM-5* were included. Treatment effectiveness was determined using the mean difference between pretreatment and posttreatment and follow-up values. Researchers described posttreatment effectiveness as either "medium-term" (ie, 3–6 months and 6–12 months) or "long-term" (ie, >12 months). Psychotherapy decreased binge-eating episodes overall and at medium-term and long-term intervals (**TABLE 1**). It also improved eating disorder psychopathology and depression but did not result in

TABLE 1. Outcomes for binge-eating disorder using psychotherapy (primarily cognitive behavioral therapy [CBT]) in a meta-analysis of 114 clinical trials[2]

Outcome	Standardized mean difference	95% CI
Binge-Eating Episodes	1.2	0.92–1.50
Overall	1.03	0.76–1.30
3–6 months	1.13	0.71–1.60
6–12 months		
Binge-Eating Episodes Abstinence	0.52	0.45–0.60
Overall	0.46	0.40– 0.60
3–6 months	0.50	0.39–0.60
6–12 months	0.50	0.19–0.80
>12 months		
Psychopathology of Eating disorder	0.90	0.70–1.10
Overall	0.85	0.52–1.20
3–6 months	0.79	0.54–1.03
6–12 months	0.89	0.51–1.26
>12 months		
Depression	0.65	0.57–0.70
Overall	0.74	0.62–0.90
3–6 months	0.69	0.57–0.80
6–12 months		
Body weight (kg)	0.28	–0.06 to 0.60
Overall	0.63	–0.25 to 1.50
3–6 months	0.25	0.13–0.40
6–12 months	0.55	–0.32 to 1.40
>12 months		
Body mass index (kg/m^2)	0.23	0.04–0.40
Overall	0.64	–0.22 to 1.50
3–6 months	0.25	0.11–0.40
6–12 months	0.48	0.10–0.90
>12 months		

TABLE 2. Abstinence rates (%) after cognitive behavioral therapy (CBT) in a comparison of several meta-analyses of patients with eating disorders[3]

	Present study		Previous meta-analyses	
	Event rate ITT[a] analysis	Event rate completer analysis	Event rate ITT analysis	Event rate completer analysis
Diagnostic group	95% CI	95% CI	95% CI	95% CI
Bulimia Nervosa	29.8 (24.9–35.3)	37.4 (29.1–46.5)	48.4 (42.4–54.5)	58.2 (49.5–66.5)
Binge-Eating Disorder	47.2 (29.8–65.2)	50.2 (29.4–70.9)	33.1 (28.0–38.6)	43.0 (35.4–51.0)
Other Specified Feeding and Eating Disorders	28.8 (18.2–42.2)	37.8 (39.0–58.8)	N/A	N/A

[a] ITT=intention to treat.

a change in weight or body mass index to a clinically meaningful degree (**TABLE 1**). The meta-analysis was limited by the lack of proper risk assessment to mitigate biases during study planning.

A 2018 meta-analysis compared outcomes of 27 nonrandomized studies of CBT for various eating disorders with rates published in previous meta-analyses of RCTs.[3] The 27 studies included 20 using individual CBT and seven providing group-based CBT; 70% of the samples had an n≥30. Included in this meta-analysis were nonrandomized trials that provided clinician-led, face-to-face CBT intervention to patients 16.5 to 41.9 years old, diagnosed with bulimia, binge-eating disorder, or "other specified feeding and eating disorders." The primary outcome was the abstinence rate from binge-eating and purging at six-month follow-up. Researchers used Hans and Hiller's clinical representativeness scale to estimate the degree to which study designed matched clinical practice. The study compared results with two previous meta-analyses of RCTs of CBT for bulimia and binge-eating disorder, separately analyzing data from all patients using intention to treat (ITT) analysis and those who completed treatment. They also examined the impact of the clinical representativeness of studies on the effect sizes and performed multiple subgroup analyses to control for factors such as publication bias, comorbidities, individual versus group-based CBT, and studies with n ≥30 versus fewer patients. The posttreatment abstinence rates for all eating disorders were higher for treatment completers compared with ITT analysis; 42.1% (95% CI, 34.7–50.0) versus 34.6% (95% CI, 29.3–40.4), similar to what was observed in the previous meta-analyses (**TABLE 2**). The abstinence rates for completer and ITT analyses were higher for binge-eating disorder compared with bulimia nervosa and "other specified feeding and eating disorders" samples (**TABLE 2**). This was in contrast with the previous meta-analyses. No correlation was observed between the degree of clinical representativeness and the effect size. EBP

Kehinde Eniola, MD, MPH, CPE, FAAFP
Jean Sykes, MPH, PhD, RD, LDN, CEDRD
Victoria Johnson Paige, DO, MS
Cone Health Family Medicine Program, Greensboro, NC

The corresponding author is Kehinde Eniola, MD, MPH, CPE, FAAFP; Kehinde.eniola@conehealth.com.
The authors declare no conflicts of interest.

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In type 2 diabetics, does insulin use increase all-cause mortality?

EVIDENCE-BASED ANSWER

No. Insulin does not increase all-cause mortality in patients with type-2 diabetes compared with oral antihyperglycemic medications (SOR: **A**, meta-analysis of randomized control trials [RCTs]). There also seems to be no mortality difference between fixed-dose and variable-dose insulin regimens (SOR: **B**, single RCT).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 meta-analysis of 26 randomized control trials (RCTs; N=24,348) evaluated insulin's effects on all-cause mortality compared with antihyperglycemic medications.[1] Patients were 48 to 67 years old, but no other demographic information was presented. Trials were included if they enrolled patients with type-2 diabetes (DM-2), involved treatment with basal insulin, and had a duration of at least 12 weeks. The intervention groups used basal insulin alone, with 69% using glargine. The control groups used different classes of antihyperglycemic medications with the two most common being glucagon-like peptide 1 analogs (57%) and metformin (77%). No significant difference was observed in all-cause mortality between the insulin and antihyperglycemic medication groups (26 trials, N=24,348; relative risk 0.99; 95% CI, 0.92–1.06). A key limitation was the relatively short treatment durations (generally 12–24 weeks).

A 1999 RCT (n=823) evaluated insulin's effect on cardiovascular and noncardiovascular mortality compared with other antihyperglycemics.[2] This trial was not included in the 2021 meta-analysis above. Patient demographics were not presented. Patients were included if they were within 1 year of their DM-2 diagnosis and tolerated treatment for 4 weeks. Those who developed hypoglycemia or were symptomatic were excluded. The four groups consisted of (a) 204 patients on a first-generation sulfonylurea (tolbutamide 1.5 g daily in a divided dose, regardless of plasma glucose response), (b) 210 patients in a insulin-standard group (ISTD) with fixed-dose insulin (10–16 units of Lente dependent on body weight, regardless of plasma glucose response), (c) 204 patients in an insulin-variable group (IVAR) with titratable insulin (varied upon patient's glucose goals), and (d) 205 patients in a control group receiving a placebo pill (matched the tolbutamide group) and dietary recommendations. Patients made quarterly check-ins for 13 years to monitor for all-cause mortality. The tolbutamide group ceased collecting data 8 years into the trial because of a significant rise in cardiovascular causes of death (2.5–-fold increase). No significant differences were observed in all-cause mortality between the ISTD group and the placebo group (ISTD 9.5 vs placebo 10.2; $P=.40$) or between the IVAR group and the placebo group (IVAR 8.8 vs placebo 10.2, $P=.31$). The study was limited by treatment adherence, which was 60–70% for patients on insulin but only 55% for the placebo group. EBP

Jasmine Douglas, MD
Ryan Ratliff, MD
James Menard, MD, MBA, FAAFP
University of Texas at Tyler Health Science Center, Tyler, TX

The corresponding author is James Menard, MD; james.menard@uhtct.edu.
The authors declare no conflicts of interest.

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Can direct oral anticoagulants be safely used in patients with ESRD?

EVIDENCE-BASED ANSWER

Apixaban is an appropriate and consistently safe choice for anticoagulation in patients with end-stage renal disease when compared with warfarin (SOR: **B**, meta-analysis of cohorts and retrospective cohort). Other direct oral anticoagulants such as rivaroxaban and dabigatran have an increased risk of bleeding compared with warfarin (SOR: **B**, retrospective cohort). Decreased dosing of apixaban is associated with an increased risk of stroke and death compared with standard dose apixaban (SOR: **B**, retrospective cohort).

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A 2018 meta-analysis (N=43,850) of five retrospective cohort studies assessed the safety and efficacy of apixaban versus warfarin in patients with end-stage renal disease (ESRD) on dialysis in the United States.[1] Owing to the existing literature on superiority of apixaban, other direct oral anticoagulants were not included. Patients were adults (mean age 70 years old) with CKD stage 4 to 5 or ESRD on dialysis, and most patients had atrial fibrillation. Participants were treated with either apixaban or warfarin with an international normalized ratio (INR) goal of two to three. FDA-recommended treatment consisted of apixaban 5 mg twice daily for nonvalvular atrial fibrillation and 2.5 mg twice daily for prevention of thromboembolic recurrence in venous thromboembolism. Researchers reduced the dose if patients met two of three criteria, including age >80 years old, weight <60 kg, or serum creatinine >1.5 mg/dL. The primary safety outcome was the probability of major bleeding. Four of the five studies defined major bleeding as a symptomatic presentation, fatal bleeding, bleeding in a critical area, bleeding causing a hemoglobin decrease of at least 2 g/dL, or requiring a blood transfusion of at least two units. After pooling patients with ESRD from all five studies (N=11,070), those in the apixaban group had significantly reduced likelihood of experiencing a major bleeding event compared with the warfarin group (odds ratio [OR] 0.27; 95% CI, 0.07–0.95).

A 2018 retrospective cohort study evaluated the safety and efficacy of apixaban versus warfarin in Medicare patients (N=25,523) with ESRD on dialysis and atrial fibrillation over five years.[2] Patients were 46% women, with a mean age of 68 years old, and included a majority of warfarin-treated patients (91%) with a goal INR of two to three. Apixaban was dosed either standardly at 5 mg twice daily or reduced dose at 2.5 mg twice daily. Primary safety outcomes included death and major bleeding defined as bleeding in a critical area or need for blood transfusion. Overall, apixaban had a significantly lower risk of major bleeding compared with warfarin with a goal INR of two to three (hazard ratio [HR] 0.72; 95% CI, 0.59–0.87). Patients treated with standard dosing apixaban had significantly reduced risk of both stroke (HR 0.61; 95% CI, 0.37–0.98) and death (HR 0.64; 95% CI, 0.45–0.92) compared with those in the reduced dosing group.

A 2015 retrospective cohort study examined the prevalence and safety of rivaroxaban and dabigatran compared with warfarin in patients (N=8,589) with atrial fibrillation on chronic hemodialysis over four years.[3] Patients were 39% women, with a mean age of 71 years old, and included majority of warfarin-treated patients (94%). Treatment included dabigatran (75–150 mg twice daily) or rivaroxaban (15 or 20 mg daily) compared with warfarin with a goal INR of two to three. The primary safety outcome was major bleeding (hospitalization or death) within two years of medication initiation. The dosages varied because some patients were dose-reduced for renal impairment. Warfarin was dosed with a goal INR of two to three and was in range at least 60% of the time. Compared with warfarin patients, those treated with dabigatran (relative risk [RR] 1.5; 95% CI, 1.2–.8) and rivaroxaban (RR 1.4; 95% CI, 1.01–1.8) had significantly higher risk of major bleeding. When considering dose adjustments, patients who were prescribed the full dose of dabigatran (RR 2.9; 95% CI, 1.9–4.3) or rivaroxaban (RR 1.9; 95% CI, 1.2–3.0) had a higher risk of major bleeding than patients who were prescribed a lower dose adjusted for renal impairment. EBP

Courtney Simpkins, PharmD, BCPS
Nolan Schmitz, PharmD, BCPS
Patricia Klatt, PharmD, BCPS
Gretchen Shelesky, MD, MS
UPMC St. Margaret Family Medicine Residency and Fellowship Program, Pittsburgh, PA

The corresponding author is Gretchen Shelesky; sheleskyg@upmc.edu.
The authors declare no conflicts of interest.

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In patients with hypertension, does doubling the dose of a single agent achieve better blood pressure control than combination therapy using two agents at lower doses?

EVIDENCE-BASED ANSWER

No. Treatment with standard-dose combination therapy is five times more effective at reducing blood pressure (BP) than doubling the dose of a single agent. (SOR **A**: meta-analysis of randomized controlled trials [RCTs]). Specifically, standard-dose combination therapy with a calcium channel blocker (CCB) and angiotensin receptor blocker is associated with a two-point larger reduction in BP, a 20% higher rate of BP control and a 16% decreased risk of adverse effects compared with high-dose CCB therapy (SOR **A**: meta-analysis of RCTs).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2009 meta-analysis (42 randomized controlled trials [RCTs], N=10,968) compared the blood pressure (BP)–lowering effects of combination antihypertensive therapy against doubling the dose of a single agent.[1] Studied patients included adults (mean ages 46–72 years old) attending hypertension clinics without a history of coronary artery disease, stroke, diabetes, or renal disease. Initial pretreatment BP for patients in the trials ranged from 136 to 173 mmHg systolic BP (SBP) and 84 to 110 mmHg diastolic BP (DBP). The authors included trials comparing therapy between two drugs of the following classes: thiazide diuretics, beta blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers (CCBs). All the studies also included a placebo group. The primary outcome was SBP reduction over a 4-week to 12-week period. The authors calculated placebo-adjusted BP reduction for each drug class, then compared the reduction of combination therapies with the expected BP reduction based on the individual drug reductions being additive. In addition, for each of the classes of drug, the observed incremental effect of doubling the dose was calculated by subtracting the BP reduction at twice the standard dose from that at the standard dose. The expected effect of doubling the dose was assumed to be double the BP reduction of standard dose. These results were expressed as a ratio of the observed to expected extra BP reduction (ie, a ratio of 1.0 would indicate that the observed effect was equal to the expected additive effect of the 2 agents or doubled dose of 1). Averaging over all medication classes, the addition of a second agent was associated with a five-fold reduction in BP compared with doubling the dose of a single agent (observed/expected ratio for dual therapy 1.0; 95% CI, 0.90–1.1 vs ratio for double agent 0.22; 95% CI, 0.19-0.25). The authors did not report on safety and tolerability data. The meta-analysis was limited by the inclusion of older studies which may not reflect current guideline-based therapies, limiting applicability.

A 2017 meta-analysis (13 RCTs, N=2,371) evaluated efficacy and safety for standard-dose combination treatment with CCBs and angiotensin receptor blockers (ARBs) compared with high-dose CCB monotherapy.[2] These studies were not included in the above 2009 meta-analysis, which excluded ARB therapy. Researchers included adult patients (mean ages 53–65 years old) meeting the diagnostic criteria for hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg). The authors did not comment on specific exclusion criteria. All but three studies investigated amlodipine as the CCB (other CCB used included nifedipine, felodipine, and lacidipine) used as high-dose monotherapy compared with standard-dose combination therapy with an ARB (agents included irbesartan, losartan, telmisartan, valsartan, and fimasartin). Standard-dose therapy was defined as the typical starting dose for the studied drug (ie, amlodipine 5 mg), and high-dose therapy was defined as the maximum recommended or marketed dose for the studied drug (ie, amlodipine 10 mg). The primary efficacy outcomes were the reduction in mean SBP and DBP from baseline to the end of the treatment. Secondary outcomes included BP control rate (undefined by authors) and adverse events. Most studies ranged in duration from 6 to 8 weeks, with one study lasting 48 weeks. Standard-dose combination therapy resulted in a larger reduction in SBP (12 studies, N=2,823; weighted mean difference [WMD] −2.5; 95% CI, –3.8 to –1.3) and

DBP (WMD –2.1; 95% CI, –3.7 to –0.4) compared with high-dose CCB monotherapy. Standard-dose combination therapy was also associated with higher rates of BP control (7 studies, N=2,527; relative risk [RR] 1.2; 95% CI, 1.1–1.3) and decreased incidence of adverse reactions (5 studies, N=1,229; RR 0.84; 95% CI, 0.75–0.95). Limitations included lack of double blinding in five of the studies, which may have introduced additional bias. EBP

Arianna Sprando, PharmD
Alicia Faggioli, PharmD, BCPS
Marianne E. Koenig, PharmD, BCPS
UPMC St. Margaret FMRP, Pittsburgh PA

The corresponding author is Marianne E. Koenig, PharmD, BCPS, UPMC; koenigme2@upmc.edu.
The authors declare no conflicts of interest.

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