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EVIDENCE-BASED PRACTICE

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EVIDENCE-BASED PRACTICE
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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.

TABLE OF CONTENTS

VOL 24 | NO. 12 | December 2021

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

IN DEPTH

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HELPDESK ANSWERS

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TABLE OF CONTENTS *Continued*

SPOTLIGHT ON PHARMACY

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

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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.

DISCLOSURE
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How effective is imaging for abdominal pain in patients?

EVIDENCE-BASED ANSWER

Computed tomography (CT) has a higher sensitivity than ultrasonography in emergency room patients with appendicitis (16% higher), diverticulitis (20% higher), and urgent gynecological diagnoses (29% higher) (SOR: **B**, single head-to-head comparison trial). The use of CT reduces planned admission by 18% and increases physician's diagnostic certainty from 71% to 92% in patients with abdominal complaints (SOR: **B**, prospective cohort study). However, abdominal radiography in the emergency department in general does not add greatly in determining the etiology of symptoms (SOR: **B**, retrospective cohort study).

DOI 10.1097/EBP.0000000000001380

A 2011 head-to-head study compared the sensitivity and predictive value of computed tomography (CT) and ultrasonography (US) in common diagnoses causing acute abdominal pain.[1] Patients included nonpregnant adults 18 years old and older (N=1,021, mean age of 47 years old, 55% female) presenting to an emergency department with acute abdominal pain (>2 hours and <5 days) and underwent both CT and US, with interpretation performed by different radiologists and radiological residents. Pregnant women, patients with penetrating or blunt trauma, patients with renal colic, those in hemorrhagic shock, or those with acute abdominal aneurysm were not included. An expert panel consisting of two experienced gastrointestinal (GI) surgeons and one experienced abdominal radiologist assigned final diagnosis. Comparing US and CT, no difference was noted in sensitivity, specificity, positive predictive value, or negative predictive value for bowel obstruction, nonurgent gastrointestinal diagnoses including gastroenteritis, constipation, epiploic appendicitis, gastritis, ulcers, cholecystitis, hepatic-pancreatic-biliary disease, inflammatory bowel disorder, and pancreatitis. For several conditions, greater sensitivity was noted with CT than US: appendicitis (94% vs 76%, $P<.01$), diverticulitis (81% vs 61%, $P<.01$), and urgent gynecological issues (70% vs 41%, $P=.04$).

A 2011 prospective cohort study determined how CT affects physician's diagnostic certainty and management decisions in patients presenting with nontraumatic abdominal complaints (N=584).[2] Patient needed to be 18 years old or older (mean age 54 years old) with nontraumatic abdominal pain. Clinicians were surveyed before and after abdominal CT to determine the leading diagnosis, degree of certainty, and planned management of decisions. Physicians were queried by standardized questionnaires, consisting of different diagnoses, probability of diagnosis, and open-ended questions for procedure and treatment. The most common diagnoses pre-CT were renal colic (n=119), intestinal obstruction (n=80), no acute condition (n=77), appendicitis (n=52), and diverticulitis (n=51). No acute condition (n=174) was the most common post-CT diagnosis, followed by renal colic (n=101), intestinal obstruction (n=43), and appendicitis (n=29). CT altered the leading diagnosis in 49% of patients and increased diagnostic certainty from 71% to 92% (284/584, $P<.01$). CT reduced the number of patients undergoing observation by 42% (from 117 to 66, $P<.01$) and increased the number discharged by 55% (from 142 to 220, *P* value not provided). Overall, the use of CT reduced planned admission by 18% (440 pre-CT vs 363 post-CT, *P* value not provided). The study did not have a control group, and only patients who came in while the investigator was working were studied.

A 2008 retrospective cohort study examined the utility of abdominal radiography by reviewing all emergency department patients who underwent abdominal radiography, including CT, US, or upper GI imaging, for any specified, nontraumatic indication (N=847).[3] Patients were 15 years old and older, and 47% were male; no further demographic information was provided. The authors classified the imaging results as normal in 34% (n=300, reference group), nonspecific in 46% (n=406, odds ratio [OR] 1.5; 95% CI, 1.1–2.1), and abnormal in 19% (n=168, OR 2.0; 95% CI, 1.3–3.0). Further supplemental imaging (abdominal CT, US, or upper GI series) was performed for 436 patients (50%) within two days. Of patients with initial normal radiograph results (n=125), 72% (n=90) were found to have abnormal findings at follow-up imaging. Setting aside catheter placement imaging, abdominal radiography helped confirm the suspected diagnosis in 2% to 8% of cases

and aided in treatment plan modification without a follow-up study in 4% of patients (n=34). Study limitations included small sample size and limited description of patient demographics. EBP

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Reduce gastric cancer risk in patients with family history by eradicating H Pylori

Choi IJ, Kim CG, Lee JY, et al. Family history of gastric cancer and *Helicobacter pylori* treatment. *N Engl J Med*. 2020; 382(5):427–436. doi: 10.1056/NEJMoa1909666.

DOI 10.1097/EBP.0000000000001219

A single-center, double-blinded, randomized placebo-controlled trial evaluated the effect of *Helicobacter pylori* eradication on risk of developing gastric cancer in patients 40 to 65 years old with at least one first-degree relative with gastric cancer. There were 3,100 patients from the South Korean cancer registry assessed for eligibility with 1,838 meeting the inclusion criteria and who underwent randomization into either the *H pylori* treatment group or the placebo group. After meeting inclusion criteria and being randomized, patients underwent endoscopy to confirm *Helicobacter pylori* infection and to ensure the absence of coexisting conditions. Primary outcome data included 1,676 patients and secondary outcome data included 1,838 patients. The primary outcome was development of gastric cancer and the secondary outcomes were survival analysis and adverse events. The treatment group received a seven-day, twice daily regimen of lansoprazole 30 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg while the placebo group received matched pills, both size and taste, on the same schedule. Surveillance endoscopies were performed every two years and at close of the study. The mean duration of data collection for participants was 9.2 years. Numerous patients were excluded from primary outcome analysis because of factors such as gastric cancer identified at baseline endoscopy, nonadherence to eradication therapy, and loss to follow-up, resulting in a final pool of 832 patients in the treatment arm and 844 in the placebo arm. Gastric cancer developed in 10 of the 832 patients (1.2%) in the treatment group and 23 of the 844 patients (2.7%) in the placebo group (hazards ratio [HR] 0.45; 95% CI, 0.21–0.94; $P=.03$) with a number needed to treat of 65. *H pylori* eradication was achieved in 70.1% of the treatment arm and 7.1% of the placebo arm. Of the 33 cases of gastric cancer that developed during this study, 28 developed from patients with persistent infection versus five in those with eradication resulting in HR of 0.27 (95% CI, 0.10–0.70). Survival rates showed no statistically significant difference with eradication and there were increased adverse events in the treatment arm compared with placebo that were usually mild.

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 PUBMED] with the terms [*H Pylori* eradication and gastric cancer] to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: *H pylori* eradication therapy reduces the risk of gastric cancer in patients with *H pylori* infection and family history of gastric cancer. However, the number of potential patients in the United States who would benefit from this practice change is small, limiting the benefit of a policy change or change in standard of practice in primary care.

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The authors declare no conflicts of interest.
The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

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Considering a new prophylaxis regimen for recurrent bacterial vaginosis

Cohen CR, Wierzbicki MR, French AL, et al. Randomized trial of Lactin-V to prevent recurrence of bacterial vaginosis. *N Engl J Med*. 2020; 382(20):1906–1915. doi: 10.1056/NEJMoa1915254.

DOI 10.1097/EBP.0000000000001217

This was a randomized, double-blind, placebo controlled, phase 2b trial to evaluate the ability of *Lactobacillus crispatus CTV-05* (Lactin-V) to prevent the recurrence of bacterial vaginosis (BV). Participants included in the trial were women ages 18 to 45 years old who had completed a course of vaginal metronidazole gel in the previous 48 hours. Subjects were excluded if they did not meet three of four Amsel criteria, if they had a Nugent score of <4 or if they were positive at the time for any of the following sexually transmitted diseases: HIV, rapid plasma reagin, gonorrhea, chlamydia, or trichomonas. A total of 228 women who met criteria were randomly assigned in a 2:1 ratio to treatment with vaginally administered Lactin-V (152 women) or placebo (76 women) for 11 weeks. Follow-up occurred through week 24 with clinic follow-up visits scheduled at four, eight, 12, and 24 weeks after enrollment. The primary outcome measured was the percentage of women who had a recurrence of BV by week 12. Secondary outcomes measured were recurrence of BV at any follow-up visit, percent of participants with detectable Lactin-V at 12 and 24 weeks, and adherence of Lactin-V regimen (number of participants who used the medication for the entire trial).

Of the total 228 women who underwent randomization, 88% of Lactin-V group and 84% of the placebo group could be evaluated for the primary outcome. In the intention-to-treat population, the primary outcome of recurrence of BV by 12 weeks occurred in 30% of the Lactin-V group and in 45% of the placebo group. The risk ratio after accounting for missing responses was 0.66; 95% CI, 0.44 to 0.87; $P=.001$. The risk ratio for recurrence by week 24, including accounting for missing responses, was 0.73; 95% CI, 0.54 to 0.92. At the 12-week visit, *Lactobacillus crispatus CTV-05* was able to be detected in 79% of participants in Lactin-V group. No significant difference was noted in the percent of participants in either the Lactin-V group or the placebo group who had at least one adverse side effect by week 24. A similar percentage of local or systemic adverse side effects was noted in both the Lactin-V and the placebo group.

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 DynaMed, UpToDate, ACOG and USPSTF with the terms bacterial vaginosis, BV, probiotics, and BV recurrence to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: This study shows that the use of Lactin-V after treatment of BV with vaginal metronidazole gel results in a statistically significant lower incidence of recurrence of BV than placebo at 12 weeks with benefits appearing to last until 24 weeks. More research will be needed to show how important strict versus as needed adherence to treatment regimen will result in recurrence of BV and also needed to determine how different forms of birth control or how male versus female sexual partners would affect results.

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Reduced medication burden without increased outcomes

Sheppard JP, Burt J, Lown M, et al. Effect of antihypertensive medication reduction vs usual care on short-term blood pressure control in patients with hypertension aged 80 years and older: the optimise randomized clinical trial. *JAMA*. 2020; 323(20):2039–2051.

DOI 10.1097/EBP.0000000000001254

This unblinded, randomized, parallel group, noninferiority trial evaluated whether patients at least 80 years old were able to maintain adequate blood pressure control over 12 weeks after partial antihypertensive medication reduction by their primary care physician during office visits. Physicians adhered to the National Institute for Health and Care Excellence (NICE) guidelines for medication reduction decisions for each patient, then monitored after one week to monitor blood pressure readings with a safety check at four weeks and conclusion at 12 weeks. Emphasis on initiating antihypertensive medications in NICE is calcium channel blockers, then ACE inhibitors or angiotensin II receptor blockers, followed by thiazide diuretics. Medication reduction was performed in reverse order. The primary outcome of this study was ability of patients to maintain blood pressure readings of <150/90 mmHg. Secondary outcomes included differences in blood pressure, frailty, quality of life, adverse effects, and serious adverse events. A noninferiority margin of 0.90 was chosen for the primary outcome, indicating that nine of every 10 patients who have their antihypertensive medications reduced would maintain goal blood pressure readings.

A total of 282 patients and 287 patients were randomized to the reduction group and usual care group, respectively. No differences in baseline characteristics were seen and 46% of the population was over 85 years old. Virtually all patients were White and had a low frailty score. Entering systolic blood pressure was a mean of about 130 mmHg for both groups. Overall, 229 patients (86.4%) in the intervention group and 236 patients (87.7%) in the control group had a systolic blood pressure lower than 150 mmHg at 12 weeks (adjusted risk ratio 0.98; 97.5% one-sided CI, 0.92 to ∞), which falls within the margin of noninferiority. A statistically significant increase of 3.4 mmHg in systolic blood pressure was noted in the reduction group; however, mean values at 12 weeks were 133.7 and 130.8 mmHg, respectively. No differences were noted in quality of life or frailty at the end of 12 weeks.

Methods

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

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

Bottom line: Although there was a slight increase in systolic blood pressure, no differences were noted in overall blood pressure control, adverse effects, quality of life, or frailty. These outcomes, while not patient oriented, can remind prescribers to evaluate medication regimens and consider deprescribing if appropriate.

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The authors declare no conflicts of interest.

Pills over power: Electrical direct-current therapy inferior to escitalopram for depression

Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression

Andre R. Brunoni, MD, PhD, Adriano H. Moffa, PsyD, Bernardo Sampaio-Junior, MD, et al. Trial of electrical direct-current therapy versus escitalopram for depression. N Engl J Med 2017; 376:2523-2533 DOI 10.1097/EBP.0000000000001165

KEY TAKEAWAY: Transcranial direct current stimulation (tDCS) did not show noninferiority to escitalopram in the treatment of depression.

STUDY DESIGN: Single-center, noninferiority trial, randomized double-blind, placebo-controlled, three-arm trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Major depressive disorder (MDD), a highly prevalent condition worldwide, is currently treated by both pharmacologic and nonpharmacologic means. Transcranial direct current stimulation is a noninvasive brain stimulation treatment in which electrical currents are applied to the mood regulating prefrontal cortex. This study compared escitalopram with tDCS in the treatment of MDD.

PATIENTS: Patients 18-75 years old with unipolar depression

INTERVENTION: tDCS (experimental) and escitalopram oxalate (active comparator)

CONTROL: Sham tDCS plus placebo (placebo comparator)

OUTCOME: Primary: change in Hamilton Depression Rating Scale (HDRS-17) score

METHODS BRIEF DESCRIPTION: Patients were randomly assigned to receive one of three regimens: 1) sham tDCS plus placebo (control), 2) sham tDCS plus escitalopram, and 3) active tDCS plus placebo. tDCS was administered throughout 22 total sessions over 10 weeks. The first 15 sessions were every weekday for three weeks, with the remaining seven sessions given once per week. Escitalopram was dosed at 10 mg daily for the first three weeks, then increased to 20 mg daily for the remaining seven weeks. Improvement was measured with depression rating scales at 3, 6, 8, and 10 weeks. The 17-item HDRS-17 (Hamilton Depression Rating Scale) was used to assess therapeutic efficacy (score 0-52, with higher scores indicating more depression). Prerequisite for enrollment was a minimum score of 17 at trial initiation. Any change in score from baseline to 10 weeks was considered significant for analysis. Noninferiority of tDCS was defined as the boundary of the CI of tDCS greater than 50% noninferiority margin between the placebo and escitalopram groups.

INTERVENTION (# IN THE GROUP): 91 escitalopram, 94 tDCS

COMPARISON (# IN THE GROUP): 60 double placebo

FOLLOW-UP PERIOD: 10 weeks. Additionally, two patients with acute mania after tDCS were followed up for six months to ensure resolution.

RESULTS:

Primary outcome

- Mean depression scores measured by HDRS-17 at baseline and compared with trial conclusion at 10 weeks decreased by 11.3 points in the escitalopram group, nine points in the tDCS group, and 5.8 points in the placebo group.
- Mean difference: 5.5 points between placebo and escitalopram (95% CI, 3.1–7.8), 3.2 points between placebo and tDCS (95% CI, 0.7–5.5), and –2.3 points between tDCS and escitalopram (95% CI, −4.3 to −0.4).
- Noninferiority of tDCS cannot be established as lower boundary of the CI (–4.3) is less than the prespecified noninferiority margin of 50% of difference between placebo group and escitalopram group (–2.75; $P=.69$).

LIMITATIONS:

1. Lack of a standardized tDCS treatment protocol.
2. Unblinding of several escitalopram-treated patients who correctly guessed their intervention, likely because of association with well-known side effects including sleepiness and obstipation.
3. Significant primary response was defined liberally as any change in HDRS-17 from baseline to study conclusion at 10 weeks, making it difficult to ascertain whether mean difference of –2.3 points between escitalopram and tDCS is clinically significant.
4. Lack of standardized follow-up after study conclusion.

EBP

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The author declares no conflicts of interest.

Can an IT Visit Planner improve communication and reduce clinical care gaps?

Visit planning using a waiting room health IT tool: the aligning patients and providers randomized controlled trial

Grant RW, Lyles C, Uratsu CS, et al. Visit planning using a waiting room health it tool: the aligning patients and providers randomized controlled trial. *Ann Fam Med*. 2019; 17(2):141–149. DOI 10.1097/EBP.0000000000001174

KEY TAKEAWAY: The Visit Planner, a simple waiting room Information and Technology (IT) tool, helps patients communicate their top priorities at the beginning of a visit but does not improve care gaps.

STUDY DESIGN: Randomized controlled trial.

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFO: As time during a visit with a primary care provider (PCP) is often limited, an IT tool called a Visit Planner is used to help determine priorities and improve communication. The aim is to improve the quality of care and address clinical care gaps.

PATIENTS: Adults 30 to 80 years old at eight outpatient clinics in California
INTERVENTION: Visit Planner IT Tool
CONTROL: Usual care
OUTCOME:
- Primary outcome–changes in clinical care gaps
- Secondary outcome–improvement in patients' abilities to communicate their top priorities during a visit with their PCP.

METHODS BRIEF DESCRIPTION: 1,110 patients from eight Kaiser Permanente Northern California clinics were allocated into two groups–an intervention arm and a control arm.
- The intervention group used an IT tool to identify the main goals prior to a visit with their PCP, while the control group did not use the IT tool and received the usual care.
- Eligible patients were Kaiser members for at least one year and had at least one clinical care gap, such as an uncontrolled HbA1C, an overdue cancer screening, etc.
- Eligible patients were new to their PCP's practice or had two or more chronic conditions.
- Eligible patients were 30 to 80 years old and had to speak English or Spanish.
- Patients were excluded if they had severe visual impairment or severe mental illness.
- Changes in care gaps were identified six months after the visit through a review of the patient's record.

The intervention group used an English or Spanish tablet-based IT tool in the waiting room, prior to seeing their PCP, in which patients viewed an educational video discussing the importance of communicating the top priorities of the visit up front. Patients then could choose one or two visit priorities. Their input would generate a printout for the physician.

Patients in the control group were greeted with a handout about healthy lifestyle.

Changes in clinical care gaps were categorized into overdue lab tests, overdue screenings, medication adherence, smoking cessation, not at goal for various lab metrics, and additional subcategories.

Postvisit telephone calls from the researchers to the patients were conducted within 1 week after the visit, using a validated 27-item questionnaire.

INTERVENTION (# IN THE GROUP): 556
COMPARISON (# IN THE GROUP): 554

FOLLOW UP PERIOD: six months

RESULTS:
Clinical care gaps were not significantly improved.
- There were four main care gaps documented: smoking (21.6% of participants), high systolic blood pressure (20.8% of participants), high HbA1C (18.5% of participants), and high LDL levels (17.9% of participants).

- Between study arms, there were no significant differences in outcome measures: o All baseline care gaps closed? Intervention versus control, 51.3% versus 54.1%, respectively, odds ratio (OR) 0.90, 95% CI, 0.7–1.2.
  - Any baseline care gaps closed? Intervention versus control, 61.6% versus 64.9%, respectively, OR 0.87, 95% CI, 0.6–1.2.
  - Any new care gaps opened? Intervention versus control, 22.6% versus 21.6%, respectively, OR 1.09, 95% CI, 0.7–1.6.
  - No care gaps at end of study? Intervention versus control, 39.8% versus 43.0%, respectively, OR 0.88, 95% CI, 0.6–1.2.

The IT Tool, "Visit Planner," significantly improved communication between patients and their PCPs.

- Patients in the intervention arm more frequently reported that they prepared questions for their doctors (59.5% vs 44.8% for the control arm, OR 1.8, 95% CI, 1.3–2.5).
- Patients in the intervention arm informed their doctors about their chief concerns at the beginning of the visit (91.3% vs 83.2%, OR 2.2, 95% CI, 1.3–3.6)

LIMITATIONS:

- Evaluating clinical outcomes over a period longer than six months may have demonstrated a more substantial impact on clinical management changes.
- The Visit Planner was not specifically tailored to the clinical care gap(s) of the individual patient, for example, overdue cancer screening, smoking cessation, etc. EBP

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Does access to an interpreter or language-concordant provider improve HbA1c levels in Spanish-speaking patients with diabetes?

EVIDENCE-BASED ANSWER

Yes. Having access to a language-concordant provider is associated with better glycemic control, defined as HbA1c <8.0, in Spanish-speaking patients with diabetes and limited English proficiency (SOR: **B**, prospective cohort study). Inversely, poorer glycemic control, defined as HbA1c>9.0, is associated with Latinos with limited English proficiency who had language-discordant providers (SOR: **B**; cross-sectional study).

DOI 10.1097/EBP.0000000000001291

A 2017 prospective cohort study evaluated the association between patient-provider language concordance and the glycemic control of adults with diabetes.[1] Patients (n=1,605, 55% female, mean 61 years old) self-identified for ethnicity, preferred language, and provider continuity. Patients in the exposure group experienced a change in provider language concordance when changing providers, both discordant to concordant (n=418) and vice versa (n=301), whereas those in the comparison group did not (discordant to discordant n=445; concordant to concordant n=441). Each patient's last recorded HbA1c before provider switch was compared with the last value taken within 12 months postswitch. The mean time between these two measurements was approximately one year. Outcomes were measured in glycemic control (HbA1c<8%) and poor glycemic control (HbA1c>9%). The number of patients achieving glycemic control improved among preferred language Spanish speakers who switched from language discordant to concordant providers in comparison with those who switched from one language discordant provider to another (10% increase; 95% CI, 2–17%). Limitations included self-report and possible misclassification of patient English proficiency status and inability to confirm Spanish language proficiency for 30% of PCPs, resulting in exclusion of PCP and patient panel from study.

In a 2010 cross-sectional observational study randomly surveyed a race-stratified sample of members of the Kaiser Permanente Norther California Diabetes Registry for language barriers and glycemic control.[2] Patients self-identified as to ethnicity and English-speaking capacity (n=6,738; 53% Whites, 40% English-speaking Latinos, and 7% limited English proficient Latinos). Surveys were offered in five languages, including English and Spanish, and assessed several social, behavioral, and care-related factors to evaluate the association of glycemic control and limited English proficiency (LEP), in conjunction with a language-concordant physician. Baseline HbA1c was assessed for LEP Latinos with type 2 diabetes, then reassessed after one year of treatment with a new provider, who was either language concordant or discordant based on patient self-evaluation. For the study, LEP participants (n=510) were classified into three groups: LEP-concordant PCP (n=137), LEP-discordant primary care physician (n=115), and LEP-missing (no physician language data available, n=258). Poor glycemic control was defined as HbA1c greater than 9.0%. LEP Latinos with a language-discordant physician were associated with a significantly poorer glycemic control (adjusted odds ratio 2.0; 95% CI, 1.03–3.8) when compared with LEP Latinos with a language-concordant physician. Study limitations included patient-reported physician concordance with no independent measure of fluency, Latino patients primarily of Mexican ancestry that might affect results compared with Latinos of other nationalities, and potential unknown differences between LEP patients with concordant providers and those with discordant providers that could influence glycemic control. EBP

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concordance and glycemic control for limited–English proficiency Latinos with type 2 diabetes. *JAMA Intern Med*. 2017; 177(3):380–395. [STEP 3]

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Do statins have a role in the treatment of Alzheimer's disease?

EVIDENCE-BASED ANSWER

No. Statins provide no improvement in memory, cognition, or executive function for patients with Alzheimer's disease (SOR: **A**, systematic review of randomized controlled trials [RCTs] and multicenter cohort). However, statin use is associated with slower memory status decline in patients with early mild cognitive impairment (SOR: **B**, multicenter cohort study).

DOI 10.1097/EBP.0000000000001339

A 2014 systematic review (N=1,154) of four randomized, double-blind trials examined the efficacy of statins on cognitive decline for patients with possible or probable Alzheimer's disease.[1] Patients were diagnosed with possible or probable Alzheimer's disease via the Neurological and Communicative Disorders and Stroke and Related Disorders Association rating scale. Those included had a mean age around 70 years old and were classified as having either mild or moderate severity dementia based on their Mini Mental State Exam (MMSE) score. Two trials treated patients with atorvastatin 80 mg daily, one trial treated patients with simvastatin 40 mg daily, and the final trial treated patients with simvastatin 80 mg, all compared with placebo. Patients in these studies were given a statin for at least six months and assessed on the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) (scored 0–70, with 0 being severe cognitive impairment and 70 being no cognitive impairment), the MMSE (scored 0–30 with 30 being no cognitive impairment and 0 being severe cognitive impairment), and treatment-related adverse events. Studies ranged from 26 to 72 weeks in length. After pooling of all four trials, patients on statins showed no significant improvements in ADAS-Cog (mean difference [MD] −0.26; 95% CI, −1.05 to 0.52), MMSE (MD −0.32; 95% CI, −0.71 to 0.06), or treatment-related adverse effects (odds ratio 1.09; 95% CI, 0.58–2.06) compared with the placebo group. No significant differences were also noted in behavior, global function, or activities of daily living between treatment groups.

A prospective 2019 multicenter cohort study (N=1,629) retrieved data from the Alzheimer's Disease Neuroimaging Initiative database to investigate associations between statin use and cognitive change.[2] All 1,629 patients were included in analysis and a total of 342 adults between the ages of 48 and 91 years old had a documented diagnosis of Alzheimer's disease. The remaining patients were categorized as cognitive normal, early mild cognitive impairment, and late mild cognitive impairment. Those with Alzheimer's disease were screened for any statin use at any dose. Statin type, dose, and duration were not reported in this study. Outcome measures included memory performance, executive function, and a global cognition score. Results were reported as parameter estimates (PEs), which can be interpreted as rate of change over time in either ADAS-Cog, memory score, or executive function score. Patients with Alzheimer's disease and statin use had no effect on memory decline (PE −0.004, P=.147), executive function (PE −0.003, P=.321), or ADAS-11 score (PE 0.078, P=.173). Although not specific for patients with Alzheimer's disease, statin use in the early mild cognitive impairment group did have a significant improvement effect on memory decline (PE 0.006, P=.019). EBP

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Is cognitive–behavioral therapy more effective than other psychotherapies in patients with schizophrenia?

EVIDENCE-BASED ANSWER

For patients with schizophrenia, cognitive–behavioral therapy (CBT) is not more effective than other forms of psychotherapy in improving risk of relapse, mental state, rehospitalization, mortality, social functioning, or quality of life, but it tends to have a lower drop out rate (SOR: **B**, meta-analyses of low- to very low-quality randomized controlled trials). The American Psychiatric Association recommends that patients with schizophrenia be treated with CBT and receive psychoeducation (SOR: **C**, expert opinion).

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A 2018 systematic review of 36 randomized controlled trials (RCTs; N=3,542) assessed the comparative effectiveness of standard care with cognitive–behavioral therapy (CBT) versus standard care with other psychotherapies for adults with schizophrenia.[1] Most of the studies were from the United Kingdom (14 trials), China (7 trials), the United States (5 trials), and Germany (4 trials); one trial each was from Australia, Canada, Italy, India, Israel, and the Netherlands. Study settings were outpatient (17 trials), inpatient (6 trials), or both (6 trials). No information was available on the study setting in six trials. The mean age of the patients ranged from 22 to 55 years old, and illness duration was between 12 weeks and 22.9 years old. The review excluded studies of patients with schizophrenia onset after age 60 years old and patients with comorbid psychotic disorders, substance-induced psychosis, significant physical or sensory difficulties, or developmental disorders and learning disabilities. Intervention group patients received standard care (eg, antipsychotic medication, hospitalization, outpatient treatment, and community psychiatric nursing care) and CBT. In 12 RCTs, patients were offered "well-defined" CBT, which was described as a psychological intervention that established a link between patients' symptoms, thoughts, or beliefs and the resulting distress or problem behaviors, leading to a reevaluation of the initial perceptions. In the remaining 24 RCTs, the definition of CBT was unclear. Patients in comparison groups also received standard care with the addition of other psychological or social interventions (eg, supportive therapy, psychoeducation, family therapy, or other talk therapy). Follow-up ranged from eight weeks to five years. CBT was not better than other psychological interventions with respect to the primary outcomes of long-term (ie, >1 year) relapse (5 trials, N=375; relative risk [RR] 1.1; 95% CI, 0.85–1.3) and long-term mental state (ie, presence or absence of symptoms of schizophrenia >1 year after treatment; 4 trials, N=249; RR 0.82; 95% CI, 0.67–1.01). No differences were also noted between CBT and the comparison treatments in the secondary outcomes of rehospitalization (8 trials, N=943), mortality (6 trials, N=627), social functioning (1 trial, n=65), and quality of life (1 trial, n=64). One modest difference was in satisfaction with treatment, defined by whether patients left the study early, which supported CBT over comparison therapies (26 trials, N=2,392; RR 0.86; 95% CI, 0.75–0.99). The review authors graded the quality of evidence as low to very low because of concerns about appropriate blinding of participants, small sample sizes, wide CIs, and using scales as surrogate measures of intended outcomes.

A 2020 consensus-based and evidence-informed practice guideline from the American Psychiatric Association (APA) recommended that patients with schizophrenia be treated with CBT for psychosis (grade 1B: recommended because the intervention clearly outweighs the harms, based on moderate quality evidence).[2] The APA guideline also recommended that patients with schizophrenia receive psychoeducation (grade 1B). EBP

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Does anticipatory prescribing of emergency contraception reduce the rate of unintended pregnancy?

EVIDENCE-BASED ANSWER

Anticipatory prescribing of emergency contraception pills (ECPs) does not reduce the unintended pregnancy rate at up to one-year follow-up (SOR: **A**, systematic review of randomized controlled trials [RCTs)] in postpartum patients; advance provision of ECPs plus lactational amenorrhea compared with lactational amenorrhea alone may lead to a small reduction in self-reported pregnancy at six-month follow-up (SOR: **B**, single RCT with limitations). The American College of Obstetrics and Gynecology recommends advance prescription of ECPs (SOR: **C**, consensus opinion).

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A 2013 systematic review and meta-analysis included four randomized controlled trials (RCTs) (N=2,792) examining the effect of advance versus standard provision of emergency contraception pills (ECPs) on pregnancy rates.[1] Women 14 to 49 years old who did not desire pregnancy were recruited from community clinics, public hospitals, and academic institutions in the United States and Hong Kong. Two trials recruited only postpartum women. One followed primarily (71%) Latina women, with a mean age of 26 years old, and the second followed primarily (94%) Black women, with a mean age of 18 years old. Intervention groups received varying ECP regimens: two packets of 1.5 mg levonorgestrel (LNG) tablets with refills, three packets of two 0.75 mg LNG tablets, eight 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol tablets, or one packet of 1.5 mg LNG. The intervention group in the fourth trial additionally received counseling and routine contraception prescription. Control group protocols varied and included counseling alone, or counseling and prescription of routine contraception if desired (1 trial). The primary outcome was pregnancy rate measured by confirmatory test and/or self-report (3 trials) at 12 months. In a pooled analysis, provision of ECPs did not reduce unintended pregnancies at six months compared with control group. Studies ranged from good to fair quality using United States Preventive Services Task Force classification. Limitations included lack of power or small sample size (2 trials), lack of blinding (1 trial), intervention and control group heterogeneity, and reliance on self-reported pregnancy data.

A 2012 Egyptian RCT (N=1,158) not included in the systematic review above assessed anticipatory prescription of LNG ECPs and pregnancy rates in postpartum, lactating women.[2] Participants included postpartum women with a mean age of 26 years old intending to breastfeed and postpone pregnancy for at least one year. Of the participants, 66% had completed secondary-level education or higher. All participants were initially counseled at delivery on use of the lactational amenorrhea method for contraception, then randomized and allocated to groups. The intervention group received one ECP dose (2 tablets LNG, 0.75 mg) at the time of counseling, whereas the control only received counseling. The primary outcome was self-reported pregnancy at six months postpartum. Provision of ECP reduced the pregnancy rate at six-month follow-up when compared with the control group (0.8% vs 5%; odds ratio [OR], 0.07; 95% CI, 0.02–0.29). Limitations included underpowering, reliance on self-reported data, and short follow-up time.

In 2017, the American College of Obstetrics and Gynecology (ACOG) recommended physicians write advance ECP prescriptions to reduce barriers to access (level C, consensus opinion).[3] ACOG had earlier acknowledged that multiple RCTs failed to demonstrate a reduction in unintended pregnancy with increased access to ECPs (level A, systematic review of RCTs).[4] EBP

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In children with ADHD, does use of stimulant medications increase the risk of sudden cardiac death?

EVIDENCE-BASED ANSWER

No. Although a slight absolute increase in overall cardiovascular events was noted in children with ADHD on stimulant medication (SOR: **B**, large retrospective cohort study), no increased risk for sudden cardiac death was noted (SOR: **B**, consistent results from 2 large retrospective cohort studies). Although the absolute risk is likely low, the risk-benefit balance of stimulants should be carefully considered.

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A 2014 Danish longitudinal, prospective cohort study examined a national cohort (n=714,258) of children born between 1990 and 1999 to assess the cardiovascular safety of stimulants in children and adolescents.[1] A subgroup of children and teenagers diagnosed with ADHD after five years old was identified (n=8,300). The mean age of ADHD diagnosis and treatment initiation was 10 years old. Any child diagnosed or beginning treatment before five years old was excluded. Dosing between children varied, but most children were dosed between 15 and 30 mg of methylphenidate. The comparison group consisted of children with an ADHD diagnosis not using stimulant medication (n=2,818). Cardiovascular events were defined as any case being treated for International Classification of Diseases codes ranging from I00 to I99 (eg, hypertension, arrhythmia, myocardial infarction, stroke, and sudden cardiac death). Stimulant treatment increased the risk of a cardiovascular events compared with nonusers of stimulant treatment (hazard ratio [HR] 2.20; 95% CI, 2.15–2.24). Cardiovascular events were rare (111 events out of 8,300 children) and none died from cardiovascular-related problems. The most common events reported were cardiovascular disease not otherwise specified (40%) and arrhythmias (23%). The major limitation in this study was the systematic information bias from ADHD subjects being followed in a hospital-affiliated outpatient clinic where they might be more likely to be identified with cardiovascular symptoms.

A United States 2011 retrospective cohort study analyzed health plan data and vital records for children and young adults 2 to 24 years old (2,579,104 person-years) to examine adverse effects across different stimulant treatments.[2] Children and adolescents 17 years old and younger currently prescribed any dose of methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine salts, atomoxetine, or pemoline (373,667 person-years) were compared with former users (607,475 person-years) and a randomly selected control group of nonusers (1,597,962 person-years) from health plan members at the same site. Mean age of included patients was 11 years old, and any patients discharged from the hospital during the preceding 365 days with a primary diagnosis of acute myocardial infarction or stroke were excluded. Serious cardiovascular events were defined as sudden cardiac death, myocardial infarction, or stroke. These events were identified from claims and vital records and adjudicated by two cardiologists or two neurologists through review of all pertinent medical records. 33 people experienced sudden cardiac death across all groups. Current users of ADHD medication were not at increased risk for sudden cardiac death (HR 0.88; 95% CI, 0.23–3.35) or for serious cardiovascular events (HR 0.75; 95% CI, 0.31–1.9) compared with nonusers. Limitations included potential confounding variables such as adherence to drug regimen or differential prescribing of ADHD drugs that could not be measured in this study. EBP

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Does a three-dose oral vitamin K regimen at birth, one week old, and one month old prevent late-onset bleeding from vitamin K deficiency?

EVIDENCE-BASED ANSWER

Most likely. Prophylaxis with three doses of oral vitamin K is associated with decreased late onset bleeding by eight newborns per 100,000 (SOR: **C**, systematic review of primarily national surveillance studies). Serum levels of vitamin K are higher with multiple oral doses of vitamin K prophylaxis compared with a single intramuscular dose measured up to two months old (SOR: **C**, disease-oriented evidence from a single randomized controlled trial in a meta-analysis).

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A 2016 systematic review of two randomized controlled trials and 13 national surveillance studies (N=5,123) examined the effectiveness of vitamin K prophylaxis on the incidence of late vitamin K deficiency bleeding (VKDB).[1] Late VKDB was defined as bleeding between eight days and one years old associated with abnormal coagulation factors that corrected with vitamin K treatment. Moderate bleeding was described as bleeding requiring treatment and severe was defined as bleeding causing damage. Two surveillance studies, one that surveyed German hospitals over a 15-month period and the other a two-year British study, using hospital report cards identified 27 and 13 infants, respectively, with late VKDB. The German study derived its denominator from the hospital surveys and the British study from census data. Newborns who were treated with 1 to 2 mg of oral vitamin K prophylaxis were significantly less likely to develop VKDB in both Germany (mean difference [MD] –80%; 95% CI, –7% to –87%) and Britain (MD –65%; 95% CI, –7% to –87%). It should be noted that rates of VKDB were very rare in both studies (1.4–7.2/100,000). A Japanese five-year national surveillance survey collected information on VKDB incidence and vitamin K prophylaxis treatment in infants. Newborns who received a prophylaxis regimen of 2 mg of oral vitamin K at one, seven, and 28 days were significantly less likely to experience VKDB compared with those without the treatment (MD –8.6 incidences per 100,000; 95% CI, –4.0 to –13 incidences per 100,000).

A 2010 meta-analysis of 13 randomized or quasi-randomized controlled trials (N=5,123) compared the efficacy of IM=intramuscular and oral vitamin K given within 12 hours of birth to each other and placebo.[2] Patients were term, low-risk, and majority breastfed newborns. Infants with any congenital malformations, or maternal treatment with vitamin K, anticoagulants, anti-tubercular, or anti-seizure medication were excluded. Late VKDB was defined as significant spontaneous or postcircumcision bleeding between 8 and 90 days old. Although the primary outcome was VKDB, the rate of bleeding was too low to determine a significant effect. One trial (N=156) that compared 2 mg of oral vitamin K at zero, seven, and 30 days in breastfeed newborns found higher vitamin K levels at two weeks (MD 0.8 ng/mL; 95% CI, 0.34–1.3 ng/mL) and two months (MD 0.3 ng/mL; 95% CI, 0.1–0.5 ng/mL) but not at one month when compared with 1 mg IM at birth. Limitations included range of dosing, vitamin K formulations used, and lack of clinical outcomes. EBP

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Does the use of external ankle bracing reduce performance in athletes?

EVIDENCE-BASED ANSWER

Probably not. External ankle bracing with either lace-up, semirigid, or adhesive tape supports has little to no effect on sprint speed, agility, vertical jump heights, and standing long jump performance in athletes (SOR: **B**, meta-analysis of randomized controlled trials [RCTs] and small individual RCTs, with inconsistent findings).

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A 2005 meta-analysis of 17 randomized controlled trials (RCTs; N=460) examined the effect of external ankle supports on lower extremity functional performance measures.[1] The patients in the studies were team sport athletes (48%) and nonathletes (32%), while the activity level for 20% of patients was not available. The average ages across studies ranged from 14.3 to 24.6 years old. Patients were predominantly male (71%); 23% were female and the gender for 6% was not reported. Most patients were healthy (61%) but 16% had an ankle injury and information on injury status for 23% was not given. External ankle support interventions included adhesive tape, a lace-up brace, or a semirigid brace; control conditions were functional performance measures without an ankle support. Outcomes were running speed, agility (ability to make quick changes in direction), and vertical jump height. In pooled data analyses, the researchers calculated standardized mean differences (SMDs), with negative results indicating performance reductions (SMD <0.2 was trivial, ≥0.2 small). Overall, external ankle supports did not affect lower extremity functional performance measures (see **TABLE**). The study was limited by the lack of an assessment of both heterogeneity and the risk of bias in the included RCTs.

A 2019 single-center crossover RCT (n=20) evaluated the consequences of ankle bracing on functional performance in athletes.[2] Participants were male (n=9) or female (n=11), current or former high school or Division I college athletes (tennis, volleyball, basketball, or soccer), involved in at least one hour per day of physical activity, five days a week, with no lower extremity injury in the preceding six weeks. Mean age was 21 years old. Participants performed three trials

TABLE. Effect of external ankle supports on lower extremity functional performance measures

Performance measure	Type of external ankle support	No. of studies	No. of patients	SMD	90% CI
Running speed	Adhesive tape	4	119	–0.14	–0.36 to 0.08
	Lace-up brace	4	55	–0.22	–0.47 to 0.03
	Semirigid brace	8	140	–0.1	–0.28 to 0.08
Agility	Adhesive tape	5	162	–0.01	–0.24 to 0.21
	Lace-up brace	5	160	0.03	–0.14 to 0.20
	Semirigid brace	12	323	0.05	–0.17 to 0.27
Vertical jump height	Adhesive tape	5	149	–0.14	– 0.37 to 0.09
	Lace-up brace	3	59	–0.04	– 0.24 to 0.16
	Semirigid brace	9	181	–0.07	– 0.2 to 0.06

Outcomes are reported as standardized mean difference (SMD), with a negative result indicating reduced performance. Data from a meta-analysis of RCTs.[1]

to test speed, jump height, and agility while wearing a traditional lace-up brace (brace 1), modified lace-up brace (brace 2), or no brace. No significant differences were noted between braced and nonbraced ankles in agility or sprint time. Ankle braces negatively affected performance (compared with no brace) of standing long jump distance (from figure: mean distance ~175 cm; mean difference brace 1 of –9.3 cm, $P=.01$, and brace 2 of –8.9 cm, $P=.01$) and vertical jump height (from figure: mean height ~50 cm; mean difference brace 1 of –1.3 cm, $P=.01$, and brace 2 of –1.3 cm, $P=.01$).

Another single-center randomized crossover trial (n=20) from 2012 assessed the effect of braced versus unbraced ankles in five male and 15 female recreational and college soccer players (average age 23 years old).[3] Participants had no ankle or lower extremity injury within the previous six months. The intervention was a lightweight lace-up ankle brace; participants acted as their own controls by performing activities both with and without the brace. Researchers measured performance in two identical session of four activities each: 1) accuracy (in cm) of kicking a soccer ball to hit a 5 × 5 cm target from 6.1 m over three attempts, 2) time to sprint 36.6 m from a standstill, 3) time to run an agility course involving four 180 degree turns, and 4) time to run, shuffle laterally left and right, and then backpedal in a "T" formation. No significant differences were noted in any of these performance measures when wearing versus not wearing the ankle brace. EBP

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Is simple reaction time a good sideline test for diagnosing concussions?

EVIDENCE-BASED ANSWER

No. Although simple reaction time using the drop-stick test and computerized reaction time are both prolonged compared with baseline in athletes diagnosed with concussions, the sensitivity and specificity of these tests alone are not sufficient to diagnose or exclude concussions (SOR: **B**, prospective cohort study and prospective observational studies).

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A 2014 prospective cohort study examined the effect of concussions on clinically measured reaction time (RT_{clin}) in college and high school athletics.[1] Patients were athletes participating in multiple sports at two universities and one high school. Patients were excluded if they were recovering from a concussion or had an upper limb injury preventing completion of the task. Investigators measured RT_{clin} at baseline during preparticipation examinations over two years by use of a clinical test that involved grasping a falling weighted measuring stick; RT_{clin} was calculated by converting the distance (cm) the stick traveled before the athlete grasped it into milliseconds (ms) using a simple mathematical formula. A mean RT_{clin} was obtained after eight trials. RT_{clin} was measured again within 48 hours of injury in 26 athletes who were physician-diagnosed with a concussion (2 with a repeat concussion). The control for each subject was an athlete from the same team who did not sustain a concussion. Repeated-measures analysis of variance was used to compare the mean baseline and follow-up RT_{clin} values between groups. RT_{clin} after injury was prolonged when compared with baseline (+17 ms; $P=.003$), whereas a trend towards

decreased RT_{clin} values was noted in the 28 controls (−9 ms, P=.058). The improvement in scores in the control group was likely because of learning effect. Using a cutoff change in score of zero milliseconds resulted in the highest sensitivity and specificity of the test (75% and 68%, respectively) with a positive likelihood ratio of 2.34 and a negative likelihood ratio of 0.37. This study was limited by the lack of blinding of the examiners, a preponderance of male athletes (22 male football players), and variability of when the test was administered (at the time of injury to up to 48 hours later).

A prospective observational study of collegiate athletes by the same author evaluated the effect of concussion on the previously described RT_{clin} with comparison to a computerized reaction time (RT_{comp}).[2] 209 athletes who were at least 18 years old were recruited from the university's football, women's soccer and wrestling teams; of these nine athletes sustained a concussion during the follow-up period. Baseline RT_{clin} and RT_{comp} were measured during the preparticipation physical examination. RT_{clin} was obtained using the same protocol as described above. RT_{comp} was obtained from the simple reaction time component of the Cogstate Sport test, which involves the presentation of single playing card face down, and the athlete must press a button as quickly as possible when the card turns face up. The nine athletes who sustained a physician-diagnosed concussion underwent repeat RT_{clin} and RT_{comp} testing within 72 hours of injury. Compared with baseline results, mean RT_{clin} was prolonged in eight of nine athletes (average 26 ms slower, P=.05), whereas mean RT_{comp} was prolonged in only five of the nine concussed athletes (average 215 ms slower, P=.21). Authors noted that previous studies in nonconcussed athletes showed anywhere from no correlation to moderate correlation between RT_{clin} and RT_{comp}. This study was limited by its small number of subjects and lack of blinding.

The test-retest reliability of the drop stick test was evaluated in a 2017 prospective observational study of 4,874 collegiate athletes.[3] Participants completed annual baseline assessments on two or three occasions to evaluate the reliability of commonly used concussion assessment tools, including RT_{clin}. Compared with year one, RT_{clin} decreased in year two (190.61 vs 198.26 ms) in 261 participants. Reliability of these results was found to be small based on an intraclass correlation coefficient of 0.32 (0.21-0.43) and an effect size of 0.34. Change scores were calculated at different CIs to be used by practitioners to provide a degree of certainty when interpreting change in performance following a suspected concussion; an increase in RT_{clin} of 10 and 29 ms correlated to confidence ranks of 75% and 90%, respectively. Improvement in reaction time was again thought to be because of learning effect. EBP

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What are the positive effects of resistance training in frail elderly patients with dementia?

EVIDENCE-BASED ANSWER

Strength training combined with moderate intensity exercise does not improve cognition in older patients with dementia. (SOR: **B**, randomized controlled trial [RCT]). Resistance training likely can improve physical capabilities such as gait characteristics including gait speed, cadence, stride length, and stride time (SOR: **C**, small RCT).

DOI 10.1097/EBP.0000000000001399

A 2018 randomized controlled trial (RCT; n=494) looked at the effect of a high-intensity exercise program on cognitive function in patients with

dementia.[1] Patients were British with an average age of 77 years old and were 61% male and predominately White (95%). All patients had a clinical diagnosis of dementia based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Patients were allocated in a 2:1 ratio (329 intervention vs 165 usual care). The intervention group completed four months of two 60- to 90-minute supervised strength and cardiovascular training sessions per week with an hour of home exercise per week. After the supervised sessions, individualized home exercise programs were created with the recommendation of continuing 150 minute of exercise per week. All patients (intervention and usual care) receive general guidance regarding dementia care to include advice regarding physical activity. The usual care group was not provided a specific exercise program. The primary outcome was the Alzheimer disease assessment scale cognition subscale (ADAS-cog, an 11-item scale, scored 0–70, with higher scores indicating worse disease) at six and 12 months. The prespecified study superiority target was 2.45 points on the ADAS-cog scale. No clinically significant difference was present between the intervention and usual care groups at six months (adjusted difference between groups –0.6; 95% CI, –1.6 to 0.4) or at 12 months (–1.4; 95% CI, –2.6 to –0.2). This study was limited by a direct intervention being limited to four months of a 12-month study.

A 2014 double-blinded RCT (n=61) evaluated whether a specific, standardized training regimen improved gait characteristics in patients with dementia.[2] Patients were 65 years old or older (mean age of 82 years old) with cognitive impairment (Mini-Mental Status Examination score of 17–26) with a confirmed dementia diagnosis who could walk 10 m without walking aid; no uncontrolled or terminal neurologic, cardiovascular, metabolic, or psychiatric disorder; and residence within 15 km of the study center. The intervention group underwent a regimen of progressive resistance and functional training for two hours, two times a week for three months with the target submaximal intensity (70–80% of 1 repetition maximum) of functionally relevant muscle groups (not defined). Control group patients met for one hour of supervised motor placebo group training twice a week for three months. Training-related improvements were noted on gait speed (mean difference [MD] 18.3 cm/s; 95% CI, 9.9–27), cadence (MD 11.16 steps/min; 95% CI, 4.4–18), stride length (MD 7.88 cm; 95% CI, 2.1–14), stride time (MD –0.08 sec; 95% CI, –0.12 to –0.03), and double support (MD –2.89% of stride time; 95% CI, –4.53 to –1.25) in the intervention group compared with the control group. No improvements were found for step width, step time variability, or walk ratio. Limitations of this study included a potential lack of generalizability to those with severe dementia since only patients with mild-to-severe dementia were included and a lack of follow-up data for the intervention on sustainability of improved gait outcomes. EBP

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Does nicotine replacement therapy in pregnancy improve smoking cessation rates and maternal and neonatal outcomes?

EVIDENCE-BASED ANSWER

The effect of nicotine replacement therapy (NRT) on smoking cessation and health outcomes in pregnant women remains uncertain. The United States Preventive Services Taskforce has concluded that the evidence is insufficient to recommend for or against NRT in pregnant women to reduce smoking cessation or improve health outcomes in pregnant women and neonates (No **SOR** given).

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A 2020 meta-analysis of nine randomized controlled trials (RCTs; N=2,336) examined the effectiveness of nicotine replacement therapy (NRT) as an adjunct to

behavioral support compared with behavioral support alone for smoking cessation in pregnant patients.[1] Trials were conducted in high-income countries in Europe, North America, and Australia with primarily English-speaking patients of European descent. Two trials had a majority of Hispanic patients and another primarily with self-identified ethnic minorities. The trial included women (16–50 years old, mean age 25–33 years old) who were at 9 to 30 weeks' gestation and had a mean self-reported cigarette use of 8 to 20 cigarettes per day. NRT included nicotine patches (7–21 mg for 16–18 hours per day, with varying degrees of constant, tapered, or biochemically adjusted doses), nicotine gum or lozenge (one 2 mg piece per cigarette smoked, 1 trial), and nicotine inhaler (4 mg nicotine/cartridge, single newest trial). The control groups received placebo with behavioral therapy or behavioral therapy alone. The primary outcome was self-reported cessation (typically 7-day point prevalence) validated with exhaled carbon monoxide, serum or salivary cotinine, or thiocyanate measured at 32 weeks' gestation or greater, in all but the oldest and smallest study, which measured cessation between 20 and 28 weeks' gestation. Clinically relevant secondary outcomes included miscarriage/spontaneous abortion, stillbirth, low birthweight (<2,500 g), preterm birth (<37 weeks), neonatal intensive care unit admissions, neonatal death, and congenital anomalies. Overall, NRT resulted in a 40% increase in cessation compared with the control group (9 RCTs, N=2,336; risk ratio [RR] 1.4; 95% CI, 1.1–1.7; see **TABLE**). However, in subgroup analysis of only placebo-controlled trials, the smoking cessation effect of NRT was not statistically significant (6 RCTs, N=2,063; RR 1.2; 95% CI, 0.95–1.6). Subgroup analysis of only the non–placebo-controlled trials demonstrated a large increase in cessation in the NRT group compared with control group (3 RCTs, N=273; RR 8.6; 95% CI, 2.1–36). Interaction testing was statistically significant when examining the effect of study design (placebo vs nonplacebo) and cessation outcomes, suggesting that the variability in effect estimates from the different subgroups is because of genuine subgroup differences rather than chance. However, the high-quality trials did border statistical significance. None of the secondary neonatal outcomes differed between groups (see **TABLE**). Nonserious side effects were reported and included headache, nausea, and local site reaction, but data could not be pooled. Overall, the placebo-controlled trials had low risk of bias; however, the non–placebo-controlled trials were limited by lack of blinding with resultant performance and detection biases. Limitations included low participation rates and low adherence rates (all trials reported <25% adherence with some women using NRT for only a few days).

In 2021, the United States Preventive Services Taskforce concluded that the current evidence on pharmacotherapy for smoking cessation in pregnant women is insufficient.[2] The taskforce stated that the evidence for NRT was limited because of a paucity of studies, such that the balance of

TABLE. NRT effect on smoking cessation in pregnancy and perinatal health outcomes[1]

	No. of trials	No. of patients	Relative risk (95% CI)
Biochemically validated smoking cessation			
Pooled analyses	9	2,336	1.4 (1.1–1.7)
Placebo-controlled trials	6	2,063	1.2 (0.95–1.6)
Non–placebo-controlled trials	3[a]	273	8.5 (2.1–35.7)
Neonatal outcomes			
Miscarriage and spontaneous abortion	5[a]	1,916	1.6 (0.5–4.8)
Stillbirth	4[a]	1,777	1.2 (0.5–2.8)
Low birth weight (<2,500 g)	7[a]	2,171	0.7 (0.4–1.2)
Preterm birth (<37 wk)	7[a]	2,182	0.8 (0.6–1.1)
Neonatal intensive care unit admission	4[a]	1,756	0.9 (0.6, 1.3)
Neonatal death	4[a]	1,746	0.7 (0.2–2.6)
Congenital abnormalities	2	1,401	0.7 (0.4–1.5)

[a] Includes non–placebo-controlled trials. NRT=nicotine replacement therapy.

benefits and harms could not be determined (I statement, insufficient evidence). EBP

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In patients with moderate or severe COPD, what are the benefits and risks of adding ICDs to combined LABA and LAMA therapy?

EVIDENCE-BASED ANSWER

In patients with moderate or severe COPD warranting combined long-acting beta-agonist and long-acting muscarinic antagonist (LAMA) therapy, the addition of inhaled corticosteroids (ICSs) reduces the risk of exacerbations by 22% to 30% without change in mortality (SOR: **A,** meta-analyses of randomized controlled trials [RCTs] and expert opinion). However, ICS use—particularly fluticasone furoate—may increase the risk of pneumonia by up to 50% (SOR: **A,** meta-analyses of RCTs).

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A 2018 systematic review and meta-analysis of 21 randomized controlled trials (RCTs) (N=25,170) assessed the efficacy of triple therapy (long-acting beta agonist [LABA], long-acting muscarinic antagonist [LAMA], and inhaled corticosteroid [ICS]) for preventing COPD exacerbations.[1] Three of the studies specifically compared triple therapy with dual therapy with LABA/LAMA in 8,046 patients with moderate or severe COPD (forced expiratory volume in one second [FEV1] <80% of predicted value) who were followed for one year. Patients in these studies had mean ages ranging from 64.4 to 67.6 years old and two-thirds were male. Specific medications varied by study, and all were administered once or twice daily. The primary outcome was moderate or severe exacerbations, and secondary outcomes were FEV1, quality of life (using the St. George's Respiratory Questionnaire [SGRQ] score, ranging from 0 to 100, with higher scores indicating greater limitation), adverse events, pneumonia, and death. (The American Thoracic Society and the European Respiratory Society put the minimal clinically significant change on the SGQR at four points and 0.1 to 0.14 L for the FEV1.)[2] Over one year, the addition of ICS to LAMA/LABA reduced the risk of moderate or severe exacerbations (2 trials, N=7,753; relative risk [RR], 0.78; 95% CI, 0.70–0.88) and prolonged the time to first moderate or severe exacerbation (2 trials, N=7,753; hazard ratio, 0.85; 95% CI, 0.79–0.91). Triple therapy was also associated with a small improvement in FEV1 (3 trials, N=6,681; mean difference [MD], 0.04 L; 95% CI, 0.02 L to 0.07 L). Patient-reported quality of life was slightly more favorable in patients treated with triple therapy (3 trials, N=6,681; SGRQ score weighted MD, –1.8; 95% CI, –2.6 to –1.0). The rate of pneumonia was significantly higher with triple versus dual therapy (3 trials, N=8,046; RR, 1.5; 95% CI, 1.2–1.9). No significant difference in other adverse events or mortality. Limitations included variable medication and dosing regimens between studies, as well as moderate heterogeneity for the risk of exacerbation outcome (I^2=46.3%).

A second 2018 systematic review and meta-analysis included five RCTs (N=11,740) comparing triple therapy with dual LAMA/LABA therapy in patients with moderate or severe COPD (FEV1 <60% predicted).[3] The patients had a 10 or more pack-year history of smoking; the mean ages ranged from 64 to 68 years old, 71% were male, and they were followed for 26 to 52 weeks. The primary outcomes were risk of moderate or severe acute COPD exacerbation, change in FEV1, and risk of pneumonia. Patient-reported health status by SGRQ was a secondary outcome. In network meta-analyses, the addition of ICS to dual therapy with LAMA/LABA reduced the risk of moderate or severe COPD exacerbations by 30% (5 trials, N not provided;

RR effect, 0.70; 95% credible interval [CrI], 0.53–0.94; number needed to treat per year=39) and minimally increased FEV1 (5 trials, N not provided; relative effect, 0.04 L; 95% CrI, 0.02 L–0.05 L). In direct (pairwise) meta-analysis, triple therapy was slightly better than dual treatment in improving SGRQ scores (5 trials, N not provided; MD, –1.6; 95% CI, –2.2 to –1.0). The addition of ICS did not increase the risk of pneumonia in pooled analysis of the five RCTs. However, in a subset analysis of a single RCT using fluticasone furoate (N= 6,221), the number needed to harm (per year of treatment) from pneumonia was 34 (95% CI, 31–38). The limitations of this study included variability in the medication regimens studied and moderate to considerable heterogeneity in the studies included in the meta-analyses (I^2=45% to 98%). All five RCTs were industry-supported drug trials, and several of the review authors reported receiving financial assistance from pharmaceutical companies. Three of the five RCTs were included in the previously mentioned systematic review and meta-analysis.[1]

A 2020 consensus and evidence-based guideline from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) concluded that triple therapy (LABA/LAMA/ICS) decreased exacerbations and improved lung function, symptoms, and health status when compared with LAMA/LABA, ICS/LABA, or LAMA alone (evidence level A, based on well-designed RCTs).[4] The GOLD guideline defined moderate COPD exacerbations as those needing treatment with short-acting bronchodilators plus antibiotics and/or oral corticosteroids. Severe exacerbations were those requiring hospitalization or emergency room visits and possibly associated with acute respiratory failure (no evidence level provided). EBP

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What are effective mass treatment strategies for prevention of *Shistosomiasis mansoni* infections?

EVIDENCE-BASED ANSWER

Community-wide and school-based treatment regimens of praziquantel are effective mass treatment strategies for the prevention of *Shistosomiasis mansoni* infections in endemic regions (SOR: **A**, randomized controlled trials).

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A 2018 cluster randomized controlled trial (RCT) compared the impact of six mass drug administration strategies of praziquantel on *Shistosomiasis mansoni* and *Shistosomiasis haematobium* prevalence and intensity.[1] The study looked at 14,620 school children 9 to 12 years old from 150 villages, randomized into six arms, representing six strategies, in a high transmission area (Mwanza region, Tanzania). The six mass drug administration strategies include the following: arm one (years 1–4 of community-wide treatment [CWT]), arm two (years 1–2 CWT, years 3–4 school-based treatment [SBT]), arm three (years 1–2 CWT, years 3–4 holiday with no drug), arm four (years 1–4 SBT), arm five (years 1–2 SBT, years 3–4 holiday), and arm six (year 1 SBT, year 2 holiday, year 3 SBT, and year 4 holiday). CWT and SBT consisted of treatment with praziquantel; specific doses were not specified. An individual was considered positive for infection if at least one egg was found in

any of six slides from three consecutive stool samples (duplicate slides per stool sample); this was used to calculate prevalence. Mean egg counts of the six slides were calculated and multiplied by 24 to express the intensity as eggs per gram of stool. Mean prevalence and mean intensity among infected were 49% in arm three to 61% in arm five and 131 eggs per gram in arm two to 230 eggs per gram in arm five, respectively. Over the five-year study period, mean prevalence and mean intensities declined in all arms, but no significant differences were noted when compared with mean prevalence and mean intensities at year five. For example, four years daily of CWT was not superior to four years of SBT (arm 1 vs arm 4, adjusted prevalence ratio 1.0; 95% CI, 0.5–2.0 and adjusted intensity ratio 0.9; 95% CI, 0.5–1.9). Two years of treatment holiday combined with two years of daily SBT had the same impact as four years of SBT (arm 5 vs arm 4, adjusted prevalence ratio 1.4; 95% CI, 0.7–2.8 and adjusted intensity ratio 1.9; 95% CI, 0.9–3.6).

A 2017 cluster RCT compared different frequencies and timing of school-based mass drug administration schedules of praziquantel 40 mg/kg in children 9 to 12 years old from 75 villages with moderate initial prevalence of *S mansoni* infections in western Kenya.[2] Seventy-five primary schools were randomized into one of three study arms (2,304–2,486 students per arm) as follows: arm one received mass drug administration (MDA) years 1–4; arm two received MDA years 1–2 and holiday years 3–4; and arm three received MDA year one, holiday year two, MDA year three, and holiday year four. All three study arms were assessed for final evaluation in year five. Intensity was determined based on the number of slides (up to 6) available per child; raw egg counts were multiplied by 24 to estimate eggs per gram of feces. If a child had at least one egg on any of the slides, he or she was considered positive for infection; this was used to determine prevalence. Significant decrease was noted in the mean prevalence of infection over five years for all three arms: arm one year 1 mean 18 (95% CI, 13–22) versus year five mean 7 (95% CI, 4.8–9.4), arm two year one mean 18 (95% CI, 14.8–21) versus year five mean 11 (95% CI, 7.6–13), and arm three year one mean 18 (95% CI, 11.8–23.4) versus year five mean 9 (95% CI, 6.4–10.7). EBP

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What are the most effective wound care measures for diabetic foot ulcers?

EVIDENCE-BASED ANSWER

No consensus best practice is present. All pressure off-loading methods for diabetic foot ulcers prevent infections equally, and nonremovable casts prevent infections better than wound dressings alone (SOR: **B**, systematic review of moderate-quality randomized controlled trials [RCTs]). Highly absorbent dressings are no more effective than standard dressings (SOR: **B**, subanalysis of 2 RCTs from a systematic review).

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A 2013 systematic review of five randomized controlled trials (RCTs; N=219) compared differing pressure-relieving and wound care techniques for the treatment of diabetic foot ulcers.[1] Patients were mostly 50 to 65 years old and were diagnosed with either type 1 or 2 diabetes mellitus. Any patient with an active infection, nonplantar wounds, severe peripheral vascular disease, visual issues, or an amputation was excluded. Preventative treatments included removable cast walkers (walking boots), therapeutic footwear including orthotics in custom-made boots, and pressure-relieving padding. Nonremovable casts evaluated were similar to the casts described above

but had extra implementations, such as fiber glass wrapping, to make devices nonremovable. Dressings used were sterile gauze dressings. All patients from all studies were followed for 90 to 100 days to evaluate for wound healing and infection. After pooling of all five trials, patients in the nonremovable cast group had a significantly higher proportion of healed ulcers compared with those with removable casts (risk ratio [RR] 1.17; 95% CI, 1.01–1.35). Additionally, nonremovable casts reduced infections compared with wound dressings only (1 trial, n=40; 0% vs 26%, $P<.05$). A major limitation was the almost universal absence of blinding for providers and researchers that may have introduced bias.

A 2015 systematic review of 17 RCTs (N=1,220) evaluated the difference in effectiveness of various wound dressings in patients with type 1 or 2 diabetes who had a foot ulcer.[2] Two trials (N=229) specifically evaluated a newly developed hydrofiber (highly absorbent nonwoven sodium carboxymethylcellulose fibers that forms a gel on contact with wound fluid). Patients of all ages and genders with type 1 or type 2 diabetes and with a foot ulcer were included. No information regarding severity of diabetes was available. Patients were randomized to have either hydrofiber or basic wound contact dressings of nonadherent knitted viscose filament gauze. Patients were followed for 168 or 350 days to evaluate wound healing and infection. After pooling the two trials, no significant difference was noted in incidence of infections between traditional and hydrofiber wound dressings (RR 1.01; 95% CI, 0.74–1.38). EBP

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What are effective treatments for advanced castration-resistant prostate cancer marked by rapidly rising PSA?

EVIDENCE-BASED ANSWER

Recommended treatment options for patients with metastatic castration-resistant prostate cancer are abiraterone, cabazitaxel, docetaxel, enzalutamide, Ra 223, and sipuleucel-T (SOR: **B**, evidence-based guideline). Combined chemotherapy-estramustine regimens improve prostate-specific antigen (PSA) response rates compared with chemotherapy alone, without overall survival benefit (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Enzalutamide reduces time to PSA progression without overall survival benefit (SOR: **B**, low-quality meta-analysis of RCTs).

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In 2017, the European Association of Urology—European Society for Radiotherapy & Oncology—International Society of Geriatric Oncology developed evidence-based practice guidelines for treatment of prostate cancer.[1] The guidelines recommended that patients with castration-resistant prostate cancer (CRPC) be treated with life-prolonging agents including abiraterone, cabazitaxel, docetaxel, enzalutamide, radium–223, or sipuleucel-T (grade A). Further, patients with metastatic CRPC, who are candidates for cytotoxic therapy, should be offered docetaxel at 75 mg/m^2 every three weeks (grade A). The guidelines recommended clinicians base second-line treatment decisions of metastatic CRPC on pre-treatment performance status, comorbidities, and extent of disease (grade B). Evidence was based on systematic reviews of randomized controlled trials (RCTs). No limitations were reported in the guideline development, including no determination of potential

sources of bias; however, all but three of the guideline authors reported potential conflicts of interest because of industry financial ties.

A 2016 meta-analysis of nine RCTs (N=956) compared estramustine–chemotherapy to chemotherapy alone in men with CRPC.[2] Male patients were mean ages of 69–70 years old (range 41–94 years old) with favorable Eastern Cooperative Oncology Group performance status (ECOG-PS). The ECOG-PS is an assessment of baseline performance status of 0–1 on a scale of 0 to 5, higher values being worse (88–89% were rated 0–1). The presence of bony or visceral metastases was not specified. Estramustine was generally given as 280 mg orally (1 trial examined a dose of 600 mg/m^2). Chemotherapy regimens included docetaxel with or without vinorelbine, epirubicin, ixabepilone, paclitaxel, or vinblastine. Relative efficacy was assessed via indirect comparison of pooled hazard ratios (HRs) for overall survival (primary endpoint) and via pooled odd ratios for time to PSA progression (secondary endpoint). Chemotherapy combined with estramustine improved PSA response rate compared with chemotherapy alone (odds ratio 1.8; 95% CI, 1.2–2.8) but did not increase overall survival (HR 0.90; 95% CI, 0.77–1.1). Limitations included insufficient power to achieve statistical significance with regard to overall survival benefit, nonreporting of adverse events in all trials, and methodological heterogeneity between included trials.

A 2018 low-quality meta-analysis of four RCTs (N=4,070) examined the relative efficacy of treatment options in patients with metastatic, docetaxel-resistant CRPC.[3] Patients in the selected studies were of average of 69 years old (range 39–95), with overwhelmingly favorable ECOG-PS (90% were rated 0–1); the presence of bony or visceral metastases was variable (mean 51%, range 23–100%). Interventions included enzalutamide versus placebo, oral abiraterone acetate plus prednisone versus prednisone alone, parenteral radium-223 versus placebo, and parenteral cabazitaxel plus prednisone versus parenteral mitoxantrone plus prednisone. Dose, duration, and frequency were not specified. Relative efficacy was assessed via indirect comparison of pooled HR for overall survival (primary endpoint) and time to PSA progression (secondary endpoint). No significant difference in overall survival was noted on indirect comparison between abiraterone acetate and enzalutamide, abiraterone acetate and radium-223, abiraterone acetate and cabazitaxel, enzalutamide and radium-223, enzalutamide and cabazitaxel, or cabazitaxel and radium-223. Significant differences were noted in time to PSA progression in favor of enzalutamide compared with abiraterone acetate (2 trials, N=1,597; HR 2.3; 95% CI, 1.7–3.2), radium-223 (2 trials, N=1,414; HR 0.39; 95% CI, 0.30–0.51), and cabazitaxel (2 trials, N=1,178; HR 0.34; 95% CI, 0.26–0.43). Limitations included insufficient power to achieve statistical significance with regard to overall survival benefit, as well as methodological and clinical heterogeneity between included trials. EBP

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Is vitamin K2 supplementation effective in reducing fractures in adults?

EVIDENCE-BASED ANSWER

Vitamin K2 supplementation does not reduce the incidence of fractures in adults with osteoporosis compared with placebo or other nonosteoporotic drugs (SOR: **A**, a meta-analysis of randomized controlled trials [RCTs]). Concurrent treatment with vitamin K2 and risedronate does not decrease the occurrence of fractures compared with risedronate alone (SOR: **B**, single RCT). Dietary vitamin K2 intake is not associated with risk of hip fracture (SOR: **B**, a longitudinal cohort study).

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A 2019 meta-analysis of 18 randomized controlled trials (RCTs; N=8,882) evaluated menatetrenone (vitamin K2) in the management of osteoporosis.[1] Osteoporotic patients (53–76 years old, 98% female) received treatments for 2 to 4 years of vitamin K2. Trials compared vitamin K2 (45 mg/d or 90 mg/d) with alfacalcidone (0.5–1.0 μg/d), sodium etidronate (200 mg/d), calcium (calcium lactate 2 g/d or calcium aspartate 1,200 mg/d), or placebo. Primary outcomes included vertebral and nonvertebral fractures. Comparing vitamin K2 and placebo, no difference was noted in nonspecific (3 trials, N=6,079; risk ratio [RR], 0.78; 95% CI, 0.78–1.3), vertebral (5 trials, N=5,508; RR 0.87; 95% CI, 0.64–1.2), or hip fractures (2 trials, N=2,196; RR 0.67, 95% CI, 0.39–1.2). No difference was noted in fracture outcomes between vitamin K2 and alfacalcidone, sodium etidronate, or calcium. Compared with placebo or no additional drug, vitamin K2 use resulted in increased risk of adverse events (2 studies, N=1,949, RR 1.5; 95% CI, 1.1–2.0) and adverse drug reactions (4 trials, N=6,102, RR 1.3; 95% CI, 1.1–1.6). The most reported adverse events were gastrointestinal disorders and skin/subcutaneous tissue disorders. Study limitations included low generalizability, no subgroup analysis on whether vitamin K2 was used as monotherapy or as part of combination therapy, and lack of blinding in some trials.

A 2017 RCT compared the efficacy of concurrent treatment with risedronate and vitamin K2 with risedronate alone for incident fractures (n=1,874).[2] Patients were Japanese women with osteoporosis (mean age 75 years old) randomly assigned to receive combined treatment (n=931) with risedronate (2.5 mg/d or 17.5 mg/wk) and vitamin K2 (45 mg/d), or a monotherapy (n=943) with risedronate alone. Exclusion criteria included warfarin treatment, contraindication for vitamin K2 or risedronate administration, and prevalent vertebral fracture. The follow-up period was two years. No significant difference in incidence rate of any fracture was observed between the two groups (incidence rate ratio 1.1; 95% CI, 0.81–1.4). Adverse events were reported by both the combined treatment group (8.6%) and the monotherapy treatment group (5.5%). Of the 137 adverse events, 97 were adverse drug reactions.

A 2011 community-based longitudinal study assessed the association between dietary intake of vitamins K1 and K2 and risk of hip fracture.[3] Patients (n=2,807, 71–75 years old, 55% female) previously participated in the 1997–1999 Hordaland Homocysteine study in Western Norway to examine the amount of vitamin K2 consumed through diet over one year. Intake of vitamin K2 was calculated using a food database and ranged from <7.2 μg/d to >16.2 μg/d. Follow-up was until first hip fracture, death, or December 31, 2009. Mean follow-up time for those who did and did not sustain a fracture was 6.7 and 11 years. For analysis, the daily intake range was divided into quartiles (Q1=lowest intake, Q4=highest intake), with Q4 as the reference. After adjusting for sex, energy intake, smoking, body mass index, vitamin D, and calcium intake, vitamin K2 intake was not associated with hip fracture for any quartile compared with the highest quartile of intake (Q1: hazard ratio [HR] 1.0; 95% CI, 0.64–1.7; Q2: HR 1.1; 95% CI, 0.71–1.7; Q3: HR 1.2; 95% CI, 0.80–1.8). No adverse events were noted. Limitations included a population limited to Norway, data collection dependent on self-reporting, and overall low K2 levels consumed compared with other studies. EBP

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In adults with POTS, are salt tablets and oral hydration more effective for reducing symptoms than oral hydration alone?

EVIDENCE-BASED ANSWER

In patients with "brain fog" because of postural orthostatic tachycardia syndrome (POTS), aggressive hydration alone is associated with improvement in 66% of users, whereas salt tablets are associated with improvement in 54% of users (SOR: **C**, low-quality retrospective cohort study). A consensus guideline recommended oral hydration for POTS symptoms in patients suspected of having hypovolemia, and dietary salt intake of 10-12 g/d using salt tablets if fluids alone were ineffective (SOR: **C**, Consensus Guideline).

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A 2013 retrospective cohort study (n=138) evaluated symptoms of "brain fog", an ill-defined cognitive impairment in adolescents with postural orthostatic tachycardia syndrome (POTS).[1] The purpose of the study was to describe and evaluate symptoms and triggers of brain fog, as well as assess efficacy of treatments. Patients in this study were 14 to 29 years old, 88% female, and with previous diagnosis of POTS via stand or tilt table test by a physician. Patients completed a 38-question survey specifically designed for this study to evaluate frequency, severity, descriptors, triggers, and treatments of brain fog. Frequency and severity were reported on a scale of 0 to 4 and 0 to 100, respectively, with higher numbers indicating greater frequency or increased severity. Patients also completed the Wood Mental Fatigue Inventory (WMFI), scored on a scale from 0 to 36 with higher numbers representing greater mental fatigue; this was used to validate the authors' 38-question survey. Study authors reported that mean values for brain fog ratings on their 38-question survey correlated with WMFI scores ($P<.001$). Most commonly reported symptoms of brain fog included forgetfulness, difficulty thinking, focusing, and communicating as well as feeling "cloudy". In this study, 96% (132/138) of participants experienced brain fog. Most common triggers of brain fog included physical fatigue, lack of sleep, prolonged standing, dehydration, and feeling faint. In the patients who tried high fluid intake of >4 L/d (122/138 participants), 66% found improvement in brain fog symptoms. Comparatively, in patients who used salt tablets (71/138 participants, no specific dose of salt tablets reported), only 54% saw improvement in symptoms as described above. No data analysis was done on these outcomes. Other nonpharmacological interventions that study participants found to be helpful in improving brain fog included lying down and avoiding heat. The study was limited by the small number of participants, recruitment via social media advertising, all results being self-reported with no validation with medical records, and lack of statistical analysis.

In 2015, a consensus guideline was written by experts who were chosen by Heart Rhythm Society to help guide health care professionals in the treatment of postural tachycardia syndrome.[2] To identify consensus, experts had to reach an agreement as a vote of >75% on each recommendation and each recommendation uses class I, IIa, IIb, III classifications. Class I is a strong recommendation, class IIa denotes benefit probably exceeds risk, class IIb denotes benefit is equal to or possibly exceeding risk, class III is a recommendation against specific treatment because there is no net benefit or there is net harm. It was recommended that patients who are known or to be suspected of having hypovolemia should drink 2 to 3 L of water per day (class IIb). The patients described as above should also increase dietary salt intake to approximately 10 to 12 g/d if tolerated using salt tablets, if water intake alone does not relieve symptoms of POTS (Class IIb). EBP

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Does coenzyme Q10 lower blood pressure in patients with hypertension?

EVIDENCE-BASED ANSWER

Probably not to any clinically relevant degree. Coenzyme Q10 may have a small effect on lowering systolic blood pressure but has no impact on diastolic blood pressure, including in patients with preexisting metabolic disease (SOR: **C**, meta-analyses of disease-oriented studies with differing results).

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A 2016 systematic review evaluating the efficacy of coenzyme Q10 (CoQ10) for primary hypertension found two double-blind, placebo-controlled randomized controlled trials (RCTs) (N=50).[1] Patients were predominantly female (54%) ranging in age from late 15 to early 16; comorbidities were metabolic syndrome (N=30) and low serum CoQ10 levels or succinate dehydrogenase activity (N=20). All patients had a systolic blood pressure (SBP) of at least 140 mmHg if nondiabetic and 130 mmHg if diabetic. Patients with significant renal disease (serum creatinine >1.5 times normal) were excluded. The intervention was CoQ10 100 mg given either daily (N=20) or BID (N=30), while the comparator was placebo. In addition, the patients were continued on their conventional antihypertensive treatment regimens. Pooled analyses show no change in SBP (2 trials, N=50; mean difference [MD] –3.7 mmHg; 95% CI, –8.9 to 1.5 mmHg) or diastolic blood pressure (DBP) (2 trials, N=50; MD –2.0 mmHg; 95% CI, –4.9 to 0.9).

A 2018 meta-analysis of 17 RCTs (N=684) examined the benefits of CoQ10 on reducing hypertension in patients with preexisting metabolic disease.[2] Studies were from Australia and New Zealand (5 trials; N=154), Denmark (3 trials; N=91), East Asia (4 trials; N=165), India (1 trial; n=58), Iran (5 trials; N=145), and the United States (1 trial; n=71). One trial (n=31) was included in the previously mentioned systematic review.[1] Comorbidities included coronary artery disease or history of myocardial infarction (4 trials; N=178), diabetes (8 trials; N=266), nonalcoholic fatty liver disease (1 trial; n=41), and obesity or metabolic syndrome (2 trial; N=582). One trial (n=71) enrolled patients with isolated systolic hypertension and another trial included healthy patients (n=46). Patients were between 19 and 80 years old, with 13 trials (N=544) focusing predominantly on those between 40 and 70 years old. Dosages of CoQ10 ranged from 100 to 900 mg/day: 15 studies (N=582) used 100 to 200 mg, one (n=56) used 300 mg, and one (n=46) used 900 mg. Duration of therapy ranged from 4 to 24 weeks. Results were pooled and expressed as standardized mean differences (SMDs) instead of reporting blood pressure changes in mmHg. Compared with placebo, CoQ10 slightly reduced SBP (16 trials, N=628; SMD –0.30; 95% CI, –0.52 to –0.08) but had no effect on DBP (14 trials, N=578; SMD –0.08; 95% CI, –0.46 to 0.29). Limitations included moderate to high heterogeneity (I^2 of 56.2%–81.7%) and potential biases because of incomplete outcome data. EBP

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Does breastfeeding for six months or more after birth decrease the risk of childhood obesity?

EVIDENCE-BASED ANSWER

Most likely. A dose-response relationship exists between breastfeeding duration and childhood obesity (SOR: **B**, meta-analysis of cross-sectional surveys and cohort studies). Breastfeeding for 6 to 11 months is associated with a 57% decrease in risk of overfat and 54% decreased risk of overweight. Breastfeeding for 12 months or more is associated with a 55% decrease and 54% decrease in obesity risk for overfat and overweight, respectively (SOR: **B**, prospective cohort study). No significant association between breastfeeding for six months or more and obesity rates is observed in children who are 24 months old through sixth grade (SOR: **B**, longitudinal cohort study).

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A 2014 meta-analysis of 25 studies (10 cross-sectional studies and 15 cohort studies) from 12 different countries compared the effect of breastfeeding on childhood obesity.[1] Patients (N=226,508) ranged in age from 1 to 14 years old. Obesity definitions were not standardized and included 30 kg/m^2 or more and body mass index percentile of 94th or more. A dose-response relationship between breastfeeding duration and childhood obesity was observed. Some breastfeeding, but less than three months, provided a 10% decrease in obesity risk (16 studies, N=not provided; adjusted odds ratio [aOR] 0.9; 95% CI, 0.84–.095). The protective effect increased in a stepwise fashion with increasing duration of breastfeeding, with a 12% decrease in risk of obesity at 3 to 4.9 months (8 studies; N=not provided; aOR 0,88; 95% CI, 0.79–0.97), 17% at 5 to 6.9 months (9 studies, N=not provided; aOR 0.83; 95% CI, 0.76–0.9), and 21% decrease at seven months or more of breastfeeding (18 studies, N=not provided; aOR 0.79; 95% CI, 0.70–0.88). Limitations included different confounders and different obesity definitions for each individual study.

A 2019 prospective cohort study evaluated breastfeeding duration and its association with weight, fat, and blood pressure in South African children.[2] Data on all children (N=1,536, 57% girls, mean 9.3 years old), including height, weight, blood pressure, and percent body fat, were collected during a home visit by field workers. Fifty-eight percent of patients had normal body fat measurements, 35% were underfat, 2% overfat, and 5% obese. In total, 51% of mothers were HIV negative, 31% were positive during pregnancy, and 18% were positive since pregnancy. All babies were HIV negative, but 31% were HIV-exposed in utero, 18% were HIV-exposed after birth, and 51% HIV-unexposed. Each mother provided breastfeeding data through maternal recall. Percent body fat at 85th percentile or more from bioimpedance measurement was classified as overfat, including obese-fat. Overweight, including obesity, was based on BMI-for-age scores. Analysis was adjusted for breastfeeding duration, early life factors, and current life factors. Breastfeeding duration of 6 to 11 months was associated with significantly decreased odds of overfat (aOR 0.43; 95% CI, 0.21–0.91) and overweight (aOR 0.46; 95% CI, 0.26–0.82). Breastfeeding for 12 or more months showed comparable results for overfat (aOR 0.45; 95% CI, 0.22–0.91) and overweight (aOR 0.46; 95% CI, 0.26–0.79). HIV exposure was not associated with obesity measures. The major limitation to this study was maternal recall for breastfeeding duration data.

A 2017 longitudinal cohort study compared breastfeeding duration on the development of childhood obesity in 1,234 infants and families.[3] The maternal population was 79% married or living together, 77% never smoked, and 81% at or above the poverty line. Child characteristics were 51% male and 82% white. Height and weight of the children were measured by a standardized protocol at six time points: 24, 36, and 54 months, and grades 1, 3 and 6. Mean birth weight was 3,446 g in non–breast-fed patients and 3,531 g in breastfed patients. A cohort of 545 children with complete data on breastfeeding at one and six months was used to determine the relationship between breastfeeding duration and obesity. Breastfeeding duration was described as six months or more, less than six months, and never breastfed. Childhood overweight and obesity were defined as 85th percentile or greater and 95th percentile or greater BMI-for-age, respectively. Breastfeeding for six months or more compared with never breastfed was not associated with a decrease in childhood obesity (aOR 0.58; 95% CI, 0.32–1.04). Limitations to this study included data collected several years previously, lack of possible confounding data such as maternal BMI, and data that were self-reported. EBP

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Does routine episiotomy reduce severe perineal trauma?

EVIDENCE-BASED ANSWER

No, routine use of episiotomy increases the risk of perineal or vaginal trauma by 30% compared with selective use of episiotomy. (SOR: **A**, systematic review). Routine use of episiotomy is not recommended (SOR: **C**, expert opinion).

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A 2017 systemic review and meta-analysis (12 randomized controlled trials, N=6,177) assessed the effects on mother and baby of selective episiotomy compared with a policy of routine episiotomy.[1] Selective episiotomy was defined as "only if needed," and routine episiotomy was defined as "part of routine management." Patients were pregnant women 16 year old and older with a singleton gestation between 28 weeks and 42 weeks who had a vaginal birth, and no severe medical or psychiatric complications (undefined) during the pregnancy. Severe perineal trauma was defined as a third- or fourth-degree vaginal laceration. Selective episiotomy resulted in 30% fewer women experiencing severe perineal or vaginal trauma (8 trials, N=5,375; relative risk [RR], 0.7; 95% CI, 0.5–0.9; I^2=37%). There was little to no difference in perineal infection (3 trials, N=1,467; RR, 0.90; 95% CI, 0.45–1.8, I^2=0%), long-term (6 months or more) dyspareunia (3 trails, N=1,107; RR, 1.14; 95% CI, 0.8–1.5; I^2=12%), or long-term (6-month or more) urinary incontinence (3 trials, N=1,107; RR, 0.98; 95% CI, 0.67–1.4). This analysis provided limited patient demographics and poorly defined definitions for routine versus selective episiotomies.

A 2019 practice guideline from The American College of Obstetricians and Gynecologists addressed the use of routine episiotomy and its effect on severe perineal trauma.[2] The guideline was created using both evidence-based data and expert opinion. They recommend selective episiotomy use over routine episiotomy, stating that this practice is associated with a lower risk for severe perineal trauma. This was a level A recommendation based on good and consistent scientific evidence. EBP

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In children with suspected asthma, what is the best confirmatory test?

EVIDENCE-BASED ANSWER

The best confirmatory test for children with suspected asthma is spirometry, along with clinical symptoms (SOR: **C**, expert consensus opinion). Fractional exhalation of nitrogen oxide measurement may be used as an adjunct test to help in the diagnosis (SOR: **C**, 1 meta-analysis, 1 cross-sectional study, and expert opinion). An IgE=Immunoglobulin E level greater than 0.35 kU/L and interrupter respiratory resistance (Rint) of 175% may also be helpful in diagnosing asthma in children but are not currently used as diagnostic tools (SOR: **C**, retrospective cross-sectional study).

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A 2018 meta-analysis examined the diagnostic accuracy of fractional exhalation of nitrogen oxide (FeNO) for asthma in children.[1] Five low- to moderate-quality studies included adults and children, 11 included children exclusively (total N=8,474). Analysis of FeNO diagnostic accuracy was performed based on FeNO cutoff values of less than 20 and 20 to 29 ppb. FeNO cutoffs less than 20 ppb had sensitivity of 0.78, specificity of 0.79, positive likelihood ratio of 3.8, and negative likelihood ratio of 0.28 for predicting asthma. FeNO levels of 20 to 29 ppb had a sensitivity of 0.61, specificity of 0.89, positive likelihood ratio of 5.3 and negative likelihood ratio of 0.44. Higher cutoffs either were not included in the trials for children. Limitations included the inability to conduct analysis in those patients using corticosteroids and based on body mass index/weight and asthma phenotype.

A 2014 retrospective cross-sectional study (N=3,612) evaluated the predictive value of various diagnostics tests along with conventional spirometry with bronchodilator reversibility in the diagnosis of asthma.[2] The study included children 6 to 18 years old with suspected asthma who presented to an outpatient allergy clinic. Asthma was diagnosed in 2,178 children by presence of symptoms identified by questionnaire in accordance with Global Initiative for Asthma (GINA) standards, physical examination by allergy specialist, and FEV=forced expiratory volume 1 improvement of 12% or greater after 200 mg salbutamol administration. All participants underwent pulmonary function testing including interrupter respiratory resistance (Rint), specific resistance of the airways, whole-body plethysmography, FEV1/FVC=forced vital capacity, as well as immunoglobulin E (IgE) levels and FeNO measurements. Of these interventions, a serum IgE of 0.35 kU/L or greater for perennial (odds ratio [OR] 3.1; 95% CI, 2.7–3.5) and seasonal allergies (OR 2.6; 95% CI, 2.4–3), Rint of 175% (OR 1.0; 95% CI, 1.001–1.004), FeNO greater than 16 ppb (OR 1.0; 95% CI, 1.0–1.01), and FEV1/FVC less than 0.80 (OR 1.3; 95% CI, 1.0–1.7) were predictive of asthma. A subgroup analysis of asthmatic patients with allergic rhinitis, perennial, or seasonal allergies was performed evaluating FeNO and Rint. Rint remained predictive of asthma when perennial allergies were present (OR 1.6; 95% CI, 1.1–2.3) or when seasonal allergies were absent (OR 1.6; 95% CI, 1.1–2.3). Rint was also predictive of asthma whether allergic rhinitis was present (OR 1.3; 95% CI, 1–1.7) or absent (OR 1.3; 95% CI, 1.1–1.6). FeNO remained predictive only in the presence of perennial allergies (OR 1.6; 95% CI, 1.1–2.3). This study did not control for ICS=inhaled corticosteroids treatment or presence of symptoms and was limited by retrospective data collection not accounting for seasonal variation of lung function.

According to the 2020 GINA Updates to Asthma prevention and Management Guidelines, spirometry is the test of choice to confirm asthma.[3] According to the National Asthma Education and Prevention Program's expert panel's 2020 Updates to Asthma Management Guidelines, a consensus-based guideline, in children five years old and above with an uncertain diagnosis or who cannot perform spirometry, FeNO can used as adjunct to clinical diagnosis (strong recommendation, moderate quality of evidence).[4] The guideline recommended a FeNO cutoff of greater than 35 ppb to support a diagnosis of asthma for children 5 to 12 years old, stating a FeNO less than 20 ppb suggested an alternate diagnosis. EBP

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Does marijuana usage have impacts on motor and executive functioning?

EVIDENCE-BASED ANSWER

Yes, cannabis usage can cause small, short-term impairments in executive functioning and motor functioning in adolescents and young adults, although these effects diminish with abstinence greater than 72 hours (SOR: **B**, meta-analysis of cross-sectional studies). Cannabis usage is associated with small-to-moderate adverse chronic impacts on functional activity in adults, despite a 14-day abstinence period (SOR: **C**, meta-analysis of cross-sectional, longitudinal, and repeated-measures studies).

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A 2018 meta-analysis (69 cross-sectional studies, N=8,727) examined cannabis usage and the effects on neurocognitive domains in adolescents and young adults.[1] Inclusion criteria were studies with participants ages 26 years old or younger who identified their cannabis use as heavy, frequent, or problematic. The average age of the cannabis users and control patients was 21 years old, with 68% of cannabis users and 56% of controls identifying as male. The mean time of abstinence before testing was 153 hours. Studies were excluded if participants had cannabis usage as a comorbidity to polysubstance use or to other mental health disorders. All studies included at least one standardized neurocognitive test. When assessing motor function, the Grooved Pegboard Dexterity Test was used, which consists of 25 holes with randomly positioned slots. Subdomains of executive functioning (abstraction/shifting, updating/working memory, and inhibition) were assessed using the Wisconsin Card Sorting Test, n-back test, and Stop Signal Paradigm, respectively, whereas speed of information processing was assessed via the Wechsler Adult Intelligence Scale, Third Edition. The standardized mean difference (SMD) was used as the measure of effect size, with a negative value indicating worse performance in the cannabis-using group compared with control group. Small significant differences in effect sizes were noted in overall cognitive function (SMD –0.25; 95% CI, –0.32 to –0.17) and in the domains of executive functioning-abstraction/shifting (SMD –0.30; 95% CI, –0.40 to –0.20), speed of information processing (SMD –0.26; 95% CI, –0.38 to –0.15), executive functioning-inhibition (SMD –0.25; 95% CI, –0.38 to –0.13), learning (SMD –0.33; 95% CI, –0.42 to –0.24), delayed memory (SMD –0.26; 95% CI, –0.35 to –0.16), attention (SMD –0.21; 95% CI, –0.31 to –0.12), and executive functioning-updating/working memory (SMD –0.22; 95% CI, –0.31 to –0.12). Nonsignificant differences were noted in motor functioning, visuospatial, and verbal language. Follow-up analysis with length of abstinence was performed. Studies requiring >72 hours abstinence did not have a significant difference in overall cognitive function (15 studies, N=928, SMD –0.08; 95% CI, –0.22 to 0.07), whereas studies requiring <72 hours did have a significant difference (54 studies, N=7,799, SMD –0.30; 95% CI, –0.37 to –0.22). Limitations in this meta-analysis included publication bias, lack of reported participant numbers in all the pooled outcomes, variations in the measurement of cannabis usage across studies, and heterogeneity of the neurocognitive tests.

A 2016 systematic review (38 studies ranging from cross-sectional, longitudinal, and repeated measures with 2-point testing, N=2,025) examined the neurocognitive effects of cannabis in adolescents and adults after a 14-day abstinent period.[2] No studies overlapped with the above systematic review. Included studies had participants with regular cannabis consumption, control groups with no cannabis use, and a 14-day abstinent period.

Participants with chronic medical and neurological illness, severe psychiatric disorders, or substance abuse disorders were excluded. The neurocognitive tests included the Iowa Gambling Task, Planning and Sequencing Ability, Verbal Fluency, and Finger-Tapping tests. The mean effect size (*r*) was measured, whereby a higher value indicated worse performance in the cannabis-using group. Small effect size differences were noted in the domains of executive function (16 studies, N=696, *r*=0.29; 95% CI, 0.11–0.42), memory and learning (16 studies, N=834, *r*=0.23; 95% CI, 0.13–0.32), and medium effect size differences were noted for attention (10 studies, N=528, *r*=0.27; 95% CI, 0.11–0.43), and motor function (5 studies, N=183, *r*=0.48; 95% CI, 0.39–0.56). An important limitation in this systematic review was that 17 of the 38 studies were conducted by the same laboratory, which may have resulted in some bias during publication. The inclusion criteria of a 14-day abstinence period may have excluded individuals who demonstrated worse executive functioning but were unable to abstain for this amount of time. EBP

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Is immediate placement of intrauterine device more cost-effective than delayed placement?

EVIDENCE-BASED ANSWER

Yes, immediate (before discharge from the hospital) intrauterine device (IUD) placement is estimated to have a societal saving of $282,540 per 1,000 women over two years and improved quality of life (SOR: **B**, 1 cost analysis prediction model). Immediate IUD insertion is recommended by the American College of Obstetricians and Gynecologists (SOR: **C**, expert opinion).

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A 2015 decision-analysis model assessed the monetary and quality of life implications of immediate postpartum versus postpartum visit intrauterine device (IUD) placement.[1] Data required for the model came from the literature available at the Centers for Disease Control, American College of Gynecology, and the National Center for Health Statistics. An incremental cost-effectiveness ratio (the cost required to gain a single quality-adjusted life-year [QALY]) was considered cost-effective if it was less than $50,000 per QALY. QALY were estimated using a complex algorithm based on cost analyses from recent literature. Immediate postpartum IUD placement saved $282,540 per 1,000 women over two years and produced a net gain of 10 quality of life years. Immediate IUD expulsion rate would have needed to exceed 56% to no longer be cost-effective. Clinical expulsion rates are estimated at 10% to 25%. Limitations of the study included multiple assumptions made to construct the decision-tree model, including expected expulsion rates at multiple time intervals (6 weeks to a year), and likelihood of a first or second pregnancy after IUD placement. The model was also limited to a two-year projection while IUDs can have a duration of use from 3 to 10 years.

A 2017 practice guideline from the American College of Obstetricians and Gynecologists recommended immediate (before hospital discharge) insertion of IUDs after either cesarian or vaginal birth.[2] This recommendation was based on expert opinion and scientific evidence and was given a Level of Evidence rating of B (limited or inconsistent scientific evidence). EBP

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Is pre-exposure prophylaxis effective and feasible for preventing HIV transmission in adolescent males?

EVIDENCE-BASED ANSWER

Pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate and emtricitabine (200/300 mg) seems to be effective in preventing HIV transmission in adolescent men who have sex with men (MSM), but its feasibility is limited by adherence to medication (SOR: **B**, 2 small safety studies). The Society for Adolescent Health and Medicine supports the use of PrEP in young MSM (SOR: **C**, consensus guidelines).

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A 2017 multicenter, open-label, phase II safety study (n=72) in the United States examined the safety of and adherence to pre-exposure prophylaxis (PrEP) in adolescent men who have sex with men (MSM).[1] The enrolled participants were healthy, HIV-uninfected young MSM 15 to 17 years old with self-reported risk for HIV acquisition in the past six months. They received an individualized session of personalized cognitive counseling for risk reduction and were instructed to take tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) 200/300 mg by mouth daily. At each subsequent study visit (monthly for 3 months and then quarterly through week 48), patients were provided condoms and completed an Integrated Next Step Counseling module (includes exploration, problem solving, and skills building around nonbiomedical behavioral strategies) to prevent HIV. During these visits, they completed serology for HIV and toxicity, questionnaires on acceptability and adherence to PrEP, and intracellular TFV-FTC level measurements from dried blood spots. Forty-six of the initial 72 participants completed 48 weeks of follow-up. The number of patients with target TFV-FTC levels (associated with protection against rectal HIV exposure) at four, eight, 12, 24, 36, and 48 weeks was 42, 37, 38, 22, 13, and 17, respectively. Three treated patients acquired an HIV infection during the study and were all found to have TDF-FTC levels consistent with taking less than two doses per week at the likely time of acquisition.

A 2017 multicenter, open-label, PrEP demonstration project and safety study (n=200) in the United States examined the adherence to PrEP in young adult MSM.[2] Patients were healthy, HIV-uninfected young MSM 18 to 22 years old with self-reported risk for HIV acquisition within the past six months. They completed a behavioral intervention program and were instructed to take TDF/FTC daily. At each subsequent study visit (monthly for 3 months and then quarterly through week 48), patients were provided condoms and sexual health and adherence promotion through Integrated Next Step Counseling. During these visits, they also completed HIV serology, questionnaires on acceptability and adherence to PrEP, and intracellular TFV-FTC level measurements from dried blood spot. Fifty-eight of the initial 200 participants completed 48 weeks of follow-up. At 12, 24, and 48 weeks, the percentage of patients with target TFV-FTC levels where 90%, 81%, and 69%, respectively. Four patients acquired an HIV infection during the study, and none had detectable levels of TFV-DP in at the visit closest to the likely time of acquisition.

A 2018 position paper by the Society for Adolescent Health and Medicine supported the use of PrEP in young MSM and advocated for increasing access to PrEP for young MSM by addressing confidentiality and consent, expanding research in the adolescent population, incorporating PrEP into comprehensive sexual health education services, and developing tools and delivery models that increase adherence.[3] EBP

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Does ginger relieve symptoms of dyspepsia?

EVIDENCE-BASED ANSWER

Ginger and artichoke supplementation relieves the intensity and symptoms of dyspepsia after two weeks of treatment but not after four weeks (SOR: **B**, a randomized control trial [RCT]). Single doses of ginger relieve gastric emptying time by a mean difference of 5.8 minutes but do not relieve reported dyspepsia symptoms (SOR: **C**, small RCT). Ginger supplementation may relieve symptoms of dyspepsia by 35% to 73% in patients with *Helicobacter pylori*–associated dyspepsia (SOR: **C**, small prospective cohort study).

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A 2015 double-blind placebo-controlled randomized control trial (RCT; n=126) evaluated the effects of ginger and artichoke leaf extract on functional dyspepsia symptoms.[1] This study included male and female patients 18 to 70 years old with symptoms of upper abdominal pain or one or more symptoms of nausea, bloating, postprandial fullness, or early satiety for at least three months without other cause. Individuals with Gastroesophageal Reflux Disease (GERD), Inflammatory Bowel Disease, history of gastric or duodenal ulcers, cancer, pregnancy, or gastrointestinal tract surgery other than cholecystectomy were excluded. The treatment group took one capsule containing 20 mg of ginger and one capsule containing 100 mg of artichoke leaf extract before lunch and dinner for 30 days. The placebo group took identical placebo capsules. Both groups avoided Proton Pump Inhibitors, H2 blockers, NSAIDs, prokinetics, and alcohol while following a low-fat diet and avoiding spicy foods 30 days before and during the study. The primary study outcome was change in intensity of dyspepsia symptoms. Patients ranked symptoms 0 to 3: 0, worse or no improvement, to 3, completely improved. After two weeks, ginger and artichoke supplementation relieved symptoms of dyspepsia compared with placebo (increase of 1.2 vs 0.35, $P<.001$). After four weeks, no further improvement was seen (–0.18 vs –0.26, $P=.5$). Secondary outcomes were self-reported severity of dyspepsia symptoms recorded on a 4-point scale (0=none to 3=severe symptoms). After four weeks, patients in the treatment group had significantly lower scores for epigastric fullness (difference of –0.24, $P<.001$), nausea (–0.4, $P<.001$), bloating (–0.17, $P=.017$), and epigastric pain (–0.17, $P=.002$). Although these differences were statistically significant, they are of questionable clinical significance, as the absolute difference on a 4-point scale was small. No significant improvement was noted in early satiety or vomiting. No adverse effects were reported in this study. Study limitations include that the supplements were only studied in combination and that all outcomes relied on self-report by patients.

A 2011 double-blind RCT (n=11) studied the effects of ginger on gastric motility and symptoms of functional dyspepsia.[2] The study included patients diagnosed with functional dyspepsia based on the Rome III criteria of persistent abdominal pain or discomfort characterized by the presence of early satiety, bloating, nausea, and postprandial fullness present for at least six weeks within the preceding six months without biochemical or structural abnormality. Patients with GERD and those taking medications affecting gastric motility were excluded. Subjects were studied on two afternoons, seven days apart in a double-blind randomized manner. On both occasions, patients received 1.2 g of ginger or placebo

after an eight-hour fast. One hour after treatment, both groups ingested 500 mL of low-nutrient soup. Abdominal ultrasound was used to measure antral dimensions and contractions and to calculate gastric half-emptying time. Gastrointestinal symptoms were measured using a questionnaire at 10-minute intervals starting five minutes before soup ingestion to 90 minutes after soup ingestion. Participants graded symptoms on a 100-mm line from 0 mm "none" to 100 mm "excruciating symptoms." Improvement in gastric emptying time was noted with ginger compared with placebo (12.3 vs 16.1 minutes, $P \leq .05$), but no difference in bloating, discomfort, nausea, fullness, appetite, or hunger symptoms. No significant difference was noted in antral contractions, fundal dimensions, or serum concentrations of ghrelin, motilin, and Glucagon-like Peptide-1. Absolute values and statistics for most outcomes were not reported. No adverse effects were noted.

A 2019 prospective cohort pilot study (n=15) compared patient symptoms of dyspepsia and eradication of *Helicobacter pylori* before and after four weeks of ginger supplementation.[3] This study included 10 women and five men, mean age 42 years old with dyspepsia associated with *H. pylori*, diagnosed by rapid urease test during endoscopy. Patients with gastric ulcers, taking antibiotics or NSAIDs, smoking history, hepatobiliary disease, Irritable Bowel Syndrome, gastric surgery history, vomiting or anorexia, or sensitivity to ginger were excluded. Patients ingested 1 g of ginger rhizome powder tablets with meals, three times daily for four weeks. The primary aim was to measure *H. pylori* eradication, measured by stool antigen test. Fifty-three percent of patients were negative after ginger supplementation ($P=.02$). Secondary outcomes were symptoms of dyspepsia. Symptoms were assessed using a visual analog scale (0–10, with 0=no symptoms to 10=severe symptoms) before and after the 4-week trial. After ginger supplementation, patients reported improvement in gastric fullness (3.27 vs 1.67, $P=.018$), early satiety (2.47 vs 1.60, $P=.039$), nausea (3.13 vs 1.40, $P=.018$), belching (2.67 vs 1.27, $P=.016$), gastric pain (2.73 vs 0.73, $P=.003$), and gastric burn (2.40 vs 1.07, $P=.039$) but not vomiting (1.47 vs 0.87, $P=.180$). Although differences were statistically significant, they may not be clinically significant as ratings were relatively low on the 10-point scale. No adverse effects were reported. Study limitations included small sample size. EBP

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Does dexamethasone prevent symptoms of altitude sickness in adults traveling to high altitude regions?

EVIDENCE-BASED ANSWER

In adults traveling to high altitude regions, the severity of altitude sickness symptoms (also known as acute mountain sickness [AMS]) is likely reduced with dexamethasone therapy, with unclear effect on the incidence (SOR: **C**, a randomized controlled trial [RCT] and a meta-analysis of low-quality data). However, dexamethasone has been recommended as an alternative medication to prevent AMS for adult travelers at moderate to high risk of AMS (SOR: **C**, expert opinion).

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A 2017, meta-analysis of six randomized controlled trials (RCTs) with 205 participants investigated the

effects of dexamethasone on high altitude illness (HAI) in high mountain areas.[1] The studies included both healthy males and females, 16 to 62 years old, who were not on any medications. Two of the studies included individuals who had not been to high altitudes for more than four weeks before the study. Participants received either dexamethasone (2 or 4 mg) or placebo orally before ascent with repeat dosing every six or 12 hours and were monitored for acute mountain sickness (AMS) from arrival to 24 hours later. The primary outcome was the incidence of AMS, and a secondary outcome was the difference in HAI/AMS scores at high altitude. Of the six RCTs, four parallel RCTs (N=176) measured the incidence of AMS and three parallel RCTs (N=50) examined the difference in HAI/AMS scores. AMS symptoms were assessed by completion of the Environmental Symptoms Questionnaire (ESQ) to quantitate the severity of symptoms (6-point Likert scale). The incidence of AMS did not differ with the administration of dexamethasone compared with placebo (4 studies, N=176, risk ratio [RR] 0.60; 95% CI, 0.36–1.0). No difference in HAI/AMS scores occurred between dexamethasone and placebo groups (3 studies, N=50, standardized mean difference –0.46; 95% CI, –1.2 to 0.29). The quality of evidence was deemed low because of extreme heterogeneity and unclear risks of selection, performance, and detection bias.

A 2014 RCT (n=138) evaluated the effect of oral dexamethasone for the prevention of AMS after ascent to a high altitude.[2] Participants included non-Tibetan, healthy young male lowland residents (18–35 years old) and excluded those who were exposed to high altitude (>2,500 m) in the past year, who had a history of severe organic diseases, and those with contraindications to budesonide or dexamethasone. Participants were randomly assigned to three treatment groups: inhaled budesonide (200 μg BID), oral dexamethasone (4 mg BID), or placebo (each group had 46 subjects). Medication was started one day before high altitude (>2,500 m) exposure and continued till the third day of exposure. The use of other personal medications was prohibited. Symptoms related to AMS were recorded at 96 hours after high altitude exposure. Primary outcome was incidence of AMS at altitude. Secondary outcomes included rates of severe AMS, heart rate, oxygen saturation, spirometric parameters, and sleep quality. AMS was diagnosed by using the Lake Louise Scoring System; a total score of three or more in the presence of a headache was indicative of AMS. Spirometry and sleep questionnaires were obtained at 144 and 168 hours, respectively. After high altitude exposure, significantly fewer participants in the dexamethasone group developed AMS compared with the placebo group (relative risk [RR] 0.51; 95% CI, 0.30–0.86). Rates of severe AMS were lower in the dexamethasone group compared with placebo (relative risk 0.2; 95% CI, 0.06–0.61). Compared with placebo, dexamethasone treatment resulted in a lower heart rate and higher oxygen saturation at altitude). No difference in spirometric parameters and sleep quality were noted between the dexamethasone and placebo groups. Limitations of this study included slower accent, selection of a healthy patient population, and inability to generalize results to other patient populations.

According to the 2019 recommendations from Wilderness and Environmental Medicine Society (WEMS), dexamethasone can be used as an alternative medication to prevent AMS for adult travelers at moderate to high risk of AMS.[3] Recommended doses are either 2 mg every six hours or 4 mg every 12 hours (strong grade 1A recommendation, high-quality evidence, based on RCTs). The WEMS recommendation was based primarily on a 1991 RCT (n=18) that compared acetazolamide (250 mg), dexamethasone (4 mg), and placebo as prophylaxis for AMS.[4] Participants included 11 men and seven women (mean age 34.6 years old) who had not been exposed to high altitude within three weeks before the study, and who were free of cardiorespiratory disease, diabetes, sulfa drug allergy, acid peptic disease, and psychiatric illness. Participants made two separate ascents (elevation 4,392 m) two weeks apart; one ascent they were administered either acetazolamide (250 mg) or dexamethasone (4 mg) and the other placebo. All medications were administered every eight hours beginning 24 hours before the start of each climb and continued until descent from the highest point. Assessment of AMS was performed by using the ESQ at sea level (24 hours after they began taking the study medications) and during the climb (within 15 minutes of reaching designated elevations). Compared with placebo, dexamethasone treatment resulted in lower AMS cerebral (0.26 vs 1.11, $P=.025$) and respiratory symptom severity scores (0.2 vs 1.45, $P<.025$). This study was limited by extremely small sample size. EBP

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What is the preferred thiamine treatment for suspected Wernicke encephalopathy?

EVIDENCE-BASED ANSWER

It's not clear. High-dose IV thiamine offers no significant therapeutic benefits compared with lower doses (SOR: **B**, single cohort study). Current guidelines recommend using at least 200 mg intravenous thiamine hydrochloride every eight hours until no further improvement in cognition is noted (SOR: **C**, consensus guidelines).

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A 2013 systemic review assessed the efficacy of thiamine in preventing and treating the manifestations of Wernicke's encephalopathy (WE) from excess alcohol consumption to determine the optimum form, dose, and duration of treatment.[1] Any randomized controlled trial comparing thiamine with alternative interventions or comparing different thiamine regimens was used. Two studies were identified that met the inclusion criteria, but only one contained sufficient data for quantitative analysis. This trial randomly assigned patients (n=107) with diagnosed alcohol dependence at risk for WE to one of five different thiamine doses for two days. Participants were recruited by consecutive admissions to a detoxification unit. Participants had a mean age of 42 years old, had been drinking for an average of 17 years, and had consumed a mean of 303 g of alcohol per day at the time of admission. Each patient was assessed by a psychologist blinded to treatment allocation on day three of treatment using the delayed alternation test. This test is a neuropsychological test sensitive for WE that evaluates working memory by requiring participants to choose correctly between two different options. The pattern of correct answers is predictable, and success is achieved when patients correctly choose 12 responses in a row. A significant mean difference of –17.90 (in the number of total trials required to achieve success) was only observed between the lowest (5 mg daily) and highest (200 mg daily) dose trials (95% CI, –35.4 to –0.40; P=.04). No significant differences were observed when the other doses were compared with 5 mg per day, and no dose-response relationship was established between the intermediate doses. Because of the small size of each group, undisclosed allocation, high noncompletion rate (25%), short duration of treatment, and unknown reliability of the cognitive test used, the systemic review concluded that there was insufficient evidence to formulate a thiamine dosing recommendation.

A retrospective cohort study published in 2018 looked at the prescribing practices of thiamine for suspected WE in a large, academic hospital over an 18-month period.[2] This study compared the effects of prescribing high-dose IV thiamine, defined as at least 200 mg thiamine twice daily, with lower-dose regimens. In patients with encephalopathy who received IV thiamine (n=432), 70% were male, the mean age was 54 years old, and high-dose IV thiamine was administered to 20% (n=86). No association was found between IV thiamine dosage and restraints, one-to-one observation, or receipt of antipsychotic and benzodiazepine medications. A lower mortality rate was observed in the group of patients who received the high-dose treatment (2% vs 13%; P=.004). However, when the data were controlled for confounding mortality risk factors, including age, male gender, and length of stay, the association was no longer significant (P=.061). No difference was found in the length of hospital stay among the groups.

The European Federation of Neurological Societies published consensus guidelines in 2010 regarding thiamine treatment for WE.[3] Based on expert opinion, the guideline recommended 200 mg thiamine every eight hours, preferably intravenously and before any carbohydrate. The societies

recommended this be continued until no further improvement in symptoms was noted. EBP

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Is capsaicin an effective treatment for cannabinoid hyperemesis syndrome?

EVIDENCE-BASED ANSWER

Topical capsaicin, when administered with traditional antiemetics for cannabinoid hyperemesis syndrome, appears to improve symptoms but not reduce emergency department length of stay or hospitalization rates significantly. (SOR: **B**, systematic review of small case series and retrospective cohort studies). Capsaicin may reduce the need for additional antiemetic doses, is cost-effective, and does not precipitate significant side effects beyond local skin irritation (SOR: **C**, small retrospective cohort).

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A 2019 systematic review examined the effectiveness of topical capsaicin for the treatment of cannabinoid hyperemesis syndrome (CHS).[1] This review included five peer-reviewed articles (all case series and reports) and six published abstracts (2 retrospective cohort studies and four case series or reports) from 2014 to 2018. Eighteen total patients were included in the peer-reviewed publications, and 77 patients were included in the published abstracts giving a total of 95 patients, 65 of which were included in the two retrospective cohort abstracts. Patients ranged in age from 16 to 47 years old. All patients reported cyclic nausea and vomiting in the setting of chronic cannabinoid use, and many reported relief with hot showers or baths, a clinical hallmark of CHS. Patients received capsaicin topical cream in a variety of strengths (0.025%–1.5%) and with a variety of adjunctive antiemetics (serotonin antagonists, metoclopramide, and others). The cream was applied to various body surface areas, primarily the abdomen, bilateral arms, and/or back, and the frequency and number of applications varied from one treatment to every four hours. All patients in the case series and case reports (n=18) as well as abstract case reports and series (n=12) who received capsaicin experienced improvement and/or resolution of nausea, vomiting, and abdominal pain at 20 minutes to "several" hours after application. A majority of these patients also received traditional antiemetics, such as ondansetron and prochlorperazine. One retrospective cohort abstract (n=22) reported a nonsignificant reduction in the incidence of hospitalization (33% vs 62%, P=.055) in patients who received capsaicin, although emergency department (ED) length of stay was prolonged nonsignificantly by 51 minutes (95% CI, –18 to 120 minutes). The second retrospective cohort abstract in this review (n=43; discussed below in greater detail) reported a nonsignificant decrease in ED length of stay (179 vs 201 minutes; P=.33) in CHS patients who received topical capsaicin. Reported adverse effects from capsaicin in the systematic review were mild, limited to skin irritation, and did not consistently result in discontinuation of therapy. Because of the nature of the data in this review (case series/reports/conference abstracts), the authors admitted the possibility of selection bias in favor of positive results, as well as other study limitations including the lack of detailed efficacy and causality statistics, significant variability in dosing regimens, and confounding adjunctive antiemetic use.

A 2019 retrospective cohort study (n=43) included in the previously mentioned systematic review, examined the benefits of topical capsaicin administration for CHS in the ED setting.[2] This study is the most recent and largest study included in the above review. It compared ED department length of stay in a cohort of patients with a primary diagnosis of CHS with and without the use of capsaicin. The study took place across a network of EDs in the same hospital system. Patients included in the final analysis were on average 32 years old, 53% male, 56% Caucasian, and 42% African American. More than half of patients used cannabinoids daily, with 26% not reporting their frequency of use. Forty-four percent reported symptomatic relief at home with hot water bath or shower exposure, and 88% reported abdominal pain along with nausea and vomiting. Patients were excluded if an alternative diagnosis for their nausea existed or if they required inpatient admission for treatment. Patients were used as their own controls in this study; they were only included if they were treated with capsaicin during the index visit and treated for CHS without capsaicin on a prior visit. The two visits were compared to look at the primary outcome (ED length of stay) and secondary outcomes (utilization of alternative therapies and total cost of the visit). Capsaicin administration was performed in the ED by applying a one-inch strip of cream topically to the

abdomen, most commonly 0.075% capsaicin content (n=25 patients), with a range of 0.025% to 0.1%. In the capsaicin cohort, authors reported a nonsignificant decrease in median ED length of stay from 201 to 179 minutes (P=.33) but a significant decrease in adjunctive medications administered (3 vs 4 doses, P=.015). The authors also reported a decrease in total opioid use for abdominal pain in the capsaicin cohort (median dose, 12 vs 15 oral morphine equivalents per patient) but did not provide statistics for significance. No significant difference was found in medication costs between the two cohort visits, and the only reported adverse effect in the capsaicin cohort was local burning/itching at the application site. The authors reported multiple limitations in this retrospective study, including potential bias at the provider level (opioid, antiemetic, and capsaicin dosing variability), as well as issues with internal controls (patients with known diagnosis of CHS may be evaluated more quickly on subsequent ED visits). EBP

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