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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.

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A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

Matthew Snyder, DO
Mike O'Callaghan Federal Medical Center/
Nellis AFB FMR
Nellis Air Force Base, NV

Chris Vincent, MD
University of Washington FMR Program
Seattle, WA

Michael Watson, MD, FAAFP
Northwest Washington Family Medicine Residency
Bremerton, WA

Mansoo Yu, PhD
FPIN
Columbia, MO

Publication Staff

Paige Smith, BS
FPIN
Columbia, MO

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
The PURLs Surveillance System is supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

Lack of support for fecal occult blood testing outside of colorectal cancer screening

Practice changer

Use fecal occult blood testing (FOBT) only for colorectal cancer screening and not in the evaluation of adult iron-deficiency anemia (SOR: **A**, based on a meta-analysis and systematic review of 22 prospective and retrospective studies).[1]

Lee MW, Pourmorady JS, Laine L. Use of Fecal Occult Blood Testing as a Diagnostic Tool for Clinical Indications: A Systematic Review and Meta-Analysis. *Am J Gastroenterol*. 2020;115(5):662-670. doi:10.14309/ajg.0000000000000495.

DOI 10.1097/EBP.0000000000001434

Illustrative case

A 57-year-old woman presents to her primary care clinic complaining of increasing fatigue over the past month. Vital signs and electrocardiogram in the clinic are unremarkable. Laboratory studies ordered from the clinic demonstrate an iron-deficiency anemia with a hemoglobin of 10.3 g/dL, mean cell volume 71 fL, and a serum iron level of 38 μg/dL, with no other major abnormalities. Her last complete blood count, from 16 months ago, showed a hemoglobin of 13.6 g/dL. Her TSH at the same time was normal. The resident precepts the patient with you and says she plans to order a fecal occult blood test (FOBT) to evaluate for a possible gastrointestinal source of the anemia. What feedback do you provide to the resident about her plan?

Clinical context

Annual FOBT is a cost-effective tool that has been validated for colorectal cancer (CRC) screening in asymptomatic individuals. More specifically, FOBT can refer both to guaiac and to fecal immunochemical testing (FIT), with FIT being the preferred alternative to colonoscopy in average-risk patients.[2] This asymptomatic screening for CRC is currently the only validated use of the FOBT.

Despite this lack of indication, both retrospective chart reviews and physician surveys have shown that FOBT is frequently performed for diagnostic purposes in patients with a clinical suspicion for gastrointestinal bleeding. This practice is particularly common for primary care and emergency providers. Common reasons for testing include anemia, black or overtly bloody stool, abdominal pain, and changes in bowel habits, with anemia being the most common, followed by overt gastrointestinal bleeding.[3,4] Several studies have also shown that over half of patients undergoing FOBT for nonscreening purposes are taking at least one medication that is likely to impact the validity of FOBT and very few patients have documentation of appropriate dietary restrictions before testing, resulting in the potential for both false-positive and false-negative results.[5,6]

Study summary

For reporting purposes, this systematic review and meta-analysis follows the Meta-analysis of Observational Studies in Epidemiology guidelines. Systematic searches of MEDLINE and EMBASE from 1948 to March 2019 were performed to identify studies in which either guaiac or immunochemical FOBT were used as diagnostic studies. Study inclusion required a population with (1) iron deficiency anemia, ulcerative colitis, or acute diarrhea; (2) diagnostic or evaluative FOBT; and (3) subsequent reference testing (eg, endoscopy, colonoscopy, or stool culture) for definitive diagnosis. Studies were excluded if patients had overt bleeding, previous diagnostic evaluation, or altered anatomy (eg, previous bariatric surgery) for anemia studies, and other combinations of gastrointestinal symptoms or conditions. Dichotomous FOBT results (positive vs negative) and the presence or absence of outcomes on diagnostic studies (endoscopic lesions, positive stool culture, and endoscopic mucosal activity) were extracted from each study. The primary analysis was sensitivity of FOBT for the aforementioned clinical diagnoses.

Twenty-two studies met inclusion criteria: 12 studies included patients with iron deficiency anemia (N=2,529), eight included patients with ulcerative colitis (N=918), and two included patients with acute diarrhea (N=504).

In patients with anemia, meta-analysis showed that FOBT had a sensitivity of 58% (95% CI, 0.53–0.63) and a specificity of 84% (95% CI, 0.75–0.89) for detection of any endoscopically defined diagnoses. For the detection of CRC in this population, FOBT had a sensitivity of 83% (95% CI, 0.72–0.90) and a specificity of 79% (95% CI, 0.68–0.86). When analyzed separately, meta-analysis showed similar sensitivity for FIT versus guaiac-based tests (82% vs 86%, respectively) in the detection of CRC.

In patients with ulcerative colitis, FOBT had a sensitivity of 72% (95% CI, 0.57–0.84) and specificity of 80%

(95% CI, 0.67–0.89) for detection of active disease. In patients with diarrhea with positive stool culture, FOBT has a sensitivity of 39% (95% CI, 0.31–0.45) and specificity of 87% (95% CI, 0.45–0.71).

The two studies evaluating the utility of FOBT in acute diarrhea had high heterogeneity and yielded low sensitivity with a positive stool culture and, therefore, do not support using FOBT for this purpose.

What's new

This large meta-analysis confirms the previous recommendation that FOBT should not be used for purposes outside of asymptomatic colorectal cancer screening, and using FOBT for any other reason could lead to false reassurance and missed or delayed diagnoses with a negative test. Patients with unexplained iron deficiency anemia, particularly men and postmenopausal women, should undergo appropriate endoscopic evaluation for a potential gastrointestinal source of blood loss.[7–9] Without further studies, fecal calprotectin remains the test of choice to monitor for active ulcerative colitis, and stool cultures are warranted in cases of severe acute diarrhea.

Caveats

Only two of the 22 studies had a low risk of bias, primarily because of lack of clear blinding on the part of the endoscopist. A significant heterogeneity was also noted between the studies in laboratory cutoffs for anemia and iron deficiency, as well as endoscopic studies performed (colonoscopy, esophagogastroduodenoscopy, or both). Some studies included combinations of gastrointestinal symptoms as one group rather than considering diarrheal and potential ulcerative colitis symptoms separately. Further studies examining the role of FOBT in the evaluation of acute diarrhea and direct comparison with fecal calprotectin for ulcerative colitis could be of further benefit. The results of this systematic review only apply to adults.

Challenges to implementation

The biggest challenge to implementation is provider education. Those unfamiliar with the specific indications for FOBT may be quick to order FOBT, believing it to be a relatively noninvasive, low-cost step in the diagnostic process. Changing existing inappropriate practices can often be more difficult than adopting new practices; hospitals, clinics, and departments may need to provide significant, active re-education or testing restrictions to decrease inappropriate use of FOBT.

Erica S. Meisenheimer, MD, FAAFP
Derrick J. Thiel, MD
Bob Marshall, MD, MPH, MISM, FAAFP
Ashley U. Hall, MD, FAACOG
Samuel M. Tiglao, DO, FAAFP
Madigan Army Medical Center,
Joint Base Lewis-McChord,
Washington, WA

The authors declare no conflicts of interest.
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Oh my! Supplemental O_2 for acute MIs

Nyström T, James SK, Lindahl B, et al. Oxygen therapy in myocardial infarction patients with or without diabetes: A predefined subgroup analysis from the DETO2X-AMI trial. *Diabetes Care*. 2019;42(11):2032-2041.

DOI 10.1097/EBP.0000000000001450

This was a prespecified subgroup analysis of a randomized controlled trial (DETO2X-AMI) of patients with or without diabetes comparing supplemental oxygen (O_2) to ambient air for patients presenting with an acute myocardial infarction (MI). Patients identified through a national database in Sweden were eligible for inclusion of the initial randomized controlled trial if they were 30 years old or older, had symptoms of an MI for less than six hours, had an initial O_2 saturation of at least 90%, and objective evidence of MI on either electrocardiography or by elevated troponin. Patients were randomized to receive 6 L/min of O_2 or ambient air for 6 to 12 hours and followed for 365 days. The primary outcome was time to the composite of all-cause death or hospitalization for a subsequent MI or heart failure.

A total of 5,010 patients were randomized in this trial with 934 patients who had diabetes and 4,076 patients without. All patients were from Sweden with an average age of 70 years old with about 70% males. A majority of patients underwent percutaneous coronary intervention. Patient receiving supplemental O_2 had an average saturation of 99% where those in ambient air group had an average saturation of at least 96%. Patients with diabetes had higher rates of the primary endpoint compared with those without diabetes. However, comparing supplemental O_2 with ambient air in each subgroup group revealed no differences in the primary outcome. For those with diabetes, 16.2% in the supplemental O_2 group compared with 16.6% in the ambient air group had the outcome (hazard ratio [HR] 0.95; 95% CI, 0.69–1.30). For those without diabetes, 9.4% of patients in the supplemental group compared with 9.6% in the ambient air group had the outcome (HR 0.96; 95% CI, 0.79–1.18).

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: Supplemental O_2 therapy in those with saturations above 90% does not alter all-cause mortality, rehospitalization for heart failure or MI, or cardiovascular death during 1-year follow-up regardless of a diagnosis of diabetes. Additionally, the Swedish patient population studied is dissimilar to the U.S. MI population, and no clear and meaningful negative consequence was noted if supplemental O_2 is initiated.

Gregory Castelli, PharmD, BCPS, BC-ADM
UPMC St. Margaret FMRP

The author declares no conflict of interest.

Little patients, little antibiotic spectrum

Gerber JS, Ross RK, Bryan M, et al. Association of Broad- vs Narrow-Spectrum Antibiotics With Treatment Failure, Adverse Events, and Quality of Life in Children With Acute Respiratory Tract Infections. *JAMA*. 2017;318(23):2325-2336.

DOI 10.1097/EBP.0000000000001448

This study was a combination of a retrospective (n=30,159) and prospective (n=2,472) cohort trial that examined the effectiveness of broad-spectrum compared with narrow-spectrum antibiotics in pediatric patients (6 months to 12 years old) with acute respiratory tract infections. The retrospective cohort trial assessed treatment failure (defined as the patient having the same symptoms and a new antibiotic prescription) and adverse events at 14 and 30 days. The prospective cohort trial assessed child's quality of life (measured using the Pediatric Quality of Life Inventory [range 0–100]). Acute respiratory infections included acute otitis media, group A streptococcal pharyngitis, and acute sinusitis. Patients were identified by diagnosis code, antibiotic prescription, and a positive rapid strep test for patients diagnosed with strep pharyngitis. Broad-spectrum antibiotics included amoxicillin-clavulanate, cephalosporins, and macrolides, and narrow-spectrum antibiotics included penicillin and amoxicillin. In the retrospective trial, no difference was

noted in treatment failure between broad-spectrum and narrow-spectrum antibiotics (3.4% vs 3.1%; *P*=.88) and no risk difference in the full matched analysis, where patients prescribed broad-spectrum antibiotics were matched to patients prescribed narrow-spectrum antibiotics based on a propensity score from patient and clinic level characteristics (risk difference [RD] 0.3; 95% CI, –0.4 to 0.9). No difference was noted in treatment failure at 30 days between groups (8.7% vs 8.1%; *P*=.51) or in the full matched analysis (RD 0.6; 95% CI, –0.4 to 1.6). When stratified by diagnosis, patients receiving broad-spectrum antibiotics for streptococcal pharyngitis were at reduced risk for treatment failure compared with narrow-spectrum antibiotics (RD –1.3, 95% CI, –2.2 to –0.3). No difference was noted in treatment failure in patients with acute otitis media or acute sinusitis. Adverse events (diarrhea, vomiting, rash, etc) were higher at 14 days in the broad-spectrum group compared with narrow-spectrum group (3.7% vs 2.7%; *P*=.001). In the prospective analysis, broad-spectrum antibiotics had a slightly lower Pediatric Quality of Life Inventory score compared with narrow-spectrum antibiotics (90.2 vs 91.5; full-matched analysis RD –1.4; 95% CI, –2.4 to –0.4) but did not reach the prespecified four-point difference, indicating clinical significance. Broad-spectrum antibiotics were also associated with more adverse events than narrow-spectrum antibiotics (35.6% vs 25.1%; RD 12.2; 95% CI, 7.3–17.2).

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	Yes	Clinically meaningful	Yes

Bottom line: This study found that broad-spectrum antibiotics are not superior to narrow-spectrum antibiotics for pediatric respiratory infections, supporting the current practice of using the narrowest spectrum as possible when treating acute respiratory infections. This trial will help with talking points when explaining antibiotic choice to parents.

Heather Bleacher, MD
University of Colorado Family Medicine Residency
Denver, CO

The author declares no conflicts of interest.

Is torsemide better than furosemide in heart failure?

Abraham B, Megaly M, Sous M, et al. Meta-Analysis Comparing Torsemide versus Furosemide in Patients With Heart Failure. *Am J Cardiol.* 2020; 125(1):92-99.

DOI 10.1097/EBP.0000000000001210

This meta-analysis of RCTs and observational studies compared the outcomes with torsemide versus furosemide in patients with heart failure. Trials were eligible for inclusion if written in English and published between January 1996 and August 2019. All studies compared the two medications except one, which was ultimately included because the comparator group vastly used furosemide. Articles were reviewed independently by two authors and evaluated for bias. The primary outcomes for the study included all-cause mortality, cardiac mortality, hospitalization as a result of heart failure, functional status, and medication side effects. Subgroup analyses were also performed looking at observational studies versus RCTs and setting of loop diuretic initiation.

A total of nine RCTs and 10 observational studies were included. More than 63% of patients in each group had heart failure with reduced ejection fraction. Patients were equally split between NYHA classes I+II and III+IV. The torsemide arm included 4,550 patients, and the furosemide arm included 14,730 patients. Groups were not similar at baseline because more patients in the torsemide group had diabetes, hypertension, and chronic kidney disease. Notably, patients on torsemide were also less likely to be on beta-blockers (66.5% vs 74.6%) and ACE/ARBs (67.7% vs 77.3%) but more likely to be on spironolactone (46.9% vs 36.5%) and digoxin (42.4% vs 31.6%). Torsemide compared with furosemide yielded improvement in functional status 72.5% versus 58%, respectively (odd ratio [OR], 2.32; 95% CI, 1.32–4.10; NNT=5; I^2=27). Torsemide did not reduce the risk of hospitalization compared with furosemide, 10.6% versus 18.4% (odds ratio [OR], 0.72; 95% CI, 0.51–1.03; *P*=.07). Furthermore, torsemide showed lower cardiac mortality, but this was ultimately deemed to be inadequately powered. No difference in all-cause mortality was found between both groups or in medication side effects.

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	Yes	Medical care setting	Yes
Valid	No	Implementable	Yes
Change in practice	Yes	Clinically meaningful	No

Bottom line: Although torsemide was associated with improvement in functional status in patients with heart failure, torsemide use did not improve other outcomes when compared with furosemide. These conclusions were primarily based on one open-labeled observational study with a comparator group not entirely taking furosemide and likely call validity into question.

Sanketh Proddutur, MD
Gregory Castelli, PharmD, BCPS, BC-ADM
UPMC St. Margaret Family Medicine Residency Program, Pittsburgh, PA

The authors declare no conflicts of interest.

Learning to breathe deeply preop can decrease postop pulmonary problems

Boden I, Skinner EH, Browning L, et al. Preoperative physiotherapy for the prevention of respiratory complications after upper abdominal surgery: pragmatic, double blinded, multicentre randomised controlled trial. *BMJ*. 2018;360:j5916.

DOI 10.1097/EBP.0000000000001449

This prospective, double-blinded, randomized control trial of 414 elective open-abdominal surgery patients compared the effectiveness of a preoperative respiratory physiotherapy education session in reducing the incidence of postoperative pulmonary complications with a control group that received an information booklet only.

The intervention session was composed of education on the importance of starting such breathing exercises and early ambulation in the immediate postoperative period and was administered in one 30-minute session by a trained physiotherapist in preadmission clinics in Australia and New Zealand within six weeks before the surgery. Both groups received an information booklet and received early ambulation postoperatively.

The primary outcome was the incidence of a postoperative pulmonary complication (PPC) within 14 days postoperatively. Secondary outcomes included length of stay, readmissions, intensive care unit stays, all-cause mortality at six weeks and 12 months, and patient-reported quality of life (using the Short Form 36 Health Survey [SF-36]), physical function, postdischarge complications, and hospital costs.

Of the 441 patients randomized, the hazard risk reduction for the occurrence of PPCs was more than half in the intervention group at 0.48 (95% CI, 0.30–0.75; $P<.001$), the absolute risk reduction was 15% (95% CI, 7%–22%), and the number needed to treat was seven (95% CI, 5–14). No significant differences were noted in the secondary outcomes, and costs will be reported in another paper. Although some apparent differences were noted in the randomized arms in some risk areas, sensitivity analysis adjusted for age, respiratory status, and type of abdominal surgery showed the same effect.

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	Yes	Medical care setting	Yes
Valid	Yes	Implementable	No
Change in practice	Yes	Clinically meaningful	Yes

Bottom line: When patients are taught the importance of early ambulation and practice simple breathing exercises within the six weeks before their date for open abdominal surgery, they can decrease their risk of postoperative pulmonary complications. However, this type of preoperative pulmonary physiotherapy visit is not commonly available currently.

Janice L. Benson, MD
Emily White VanGompel
University of Chicago NorthShore FMRP, Glenview, IL

The author declares no conflicts of interest.

It's a TRAP! Low-income and rural women face consequences of medication abortion restriction

Medication abortion use among low-income and rural Texans before and during state-imposed restrictions and after FDA-updated labeling

Goyal V, Brooks IHM, Wallace R, et al. Medication abortion use among low-income and rural Texans before and during state-imposed restrictions and after FDA-updated labeling. *Am J Obstet Gynecol*. 2020; 223(2): 236.e1–236.e8. DOI 10.1097/EBP.0000000000001177

KEY TAKEAWAY: Restrictions on medication abortion decrease its utilization compared with procedural abortion, especially among patients with low incomes or who are traveling farther for care.
STUDY DESIGN: Case-control study
LEVEL OF EVIDENCE: STEP 3

BACKGROUND: Targeted restrictions on abortion providers (TRAP laws) hamper access to safe and legal abortion. In 2013, Texas enacted House Bill 2 (HB 2), restricting abortion access to clinics that met criteria as ambulatory surgical centers, causing multiple clinic closures. Medication abortion use was limited based on mifepristone's 2000 Food and Drug Administration (FDA) labeling (ie, clinic-administered mifepristone followed 48 hours later by clinic-administered misoprostol for pregnancy termination up to 7 weeks' of gestation). The FDA updated mifepristone's labeling in 2016, allowing self-administration of misoprostol 24 to 48 hours after clinic-administered mifepristone in pregnancies up to 10 weeks of gestation.

PATIENTS: Women obtaining abortion care in Texas
INTERVENTION: HB 2 enactment in 2013 and post-FDA update in 2016
CONTROL: Pre-HB 2 abortion data
OUTCOME: Percentage of abortions performed as medication abortion

METHODS (BRIEF DESCRIPTION):
- Data were collected from seven abortion clinics in Texas over three-year-long periods.
- Percentages were calculated for elective medication abortions compared with total abortions performed in a study period.
- Data were stratified based on patient driving distance to nearest abortion clinic (0–24 miles, 25–49 miles, 50–99 miles, or 100+ miles), availability of abortion in home county (open clinic, closed clinic, or no clinic), and patient financial status (greater than 110% Federal Poverty Level [FPL] or less than or equal to 110% FPL).
- Odds ratios (OR) for likelihood of receiving medication abortion were also calculated for the different subcategories.

INTERVENTION (# IN THE GROUP):
23,126 abortions post-HB 2
25,826 abortions post-FDA update
COMPARISON (# IN THE GROUP): 21,626 abortions pre-HB 2

FOLLOW-UP PERIOD: 2012 through 2017

RESULTS:
The proportion of medication abortions significantly dropped after HB 2 enactment but rebounded after the FDA loosened its restrictions on mifepristone/misoprostol administration.

Overall
- Pre-HB 2: 5,571 medication abortions/21,626 total abortions (26%)
- Post-HB 2: 1,631/23,126 (7%)
- Post-FDA update: 7,490/25,826 (29%)

Highlights of data by category
- Driving distance of 100+ miles compared with 0 to 24 miles:
- Pre HB 2: 290/1,514 (19%) (OR, 0.60; 95% CI, 0.52–0.68)
- Post HB 2: 31/1,825 (2%) (OR, 0.21; 95% CI, 0.15–0.30)

- Post-FDA update: 507/2,062 (25%) (OR, 0.82; 95% CI, 0.74–0.91)
- Income ≤110% Federal Poverty Level:
- Pre HB 2: 1,768/7,683 (23%) (OR, 0.98; 95% CI, 0.89–1.07)
- Post HB 2: 658/8,505 (8%) (OR, 0.76; 95% CI, 0.68–0.85)
- Post-FDA update: 2,685/9,777 (27%) (OR, 0.77; 95% CI, 0.72–0.81)

LIMITATIONS:

- Data from clinics that were not open for all three study periods were not used.
- Some clinic closures were forced post-HB 2 because of the lack of Ambulatory Surgical Center designation, preventing adequate comparisons of pre- and post- HB 2 data for those centers, despite those being likely sites for higher use of medication abortion.
- The study did not account for the subset of patients unable to obtain desired clinical abortion care, nor patients who sought care outside of clinical medicine. EBP

Audrey Coates, MD
CMU Family Medicine Residency Program
Saginaw, MI

The author declares no conflicts of interest.

Outpatient COVID-19 Treatment: Are Antibodies the Answer?

SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19

Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. *N Engl J Med* 2021;384(3):229-237. DOI 10.1097/EBP.0000000000001382

KEY TAKEAWAY: Outpatient treatment with 2,800 mg of LY-CoV555, a neutralizing antibody, in patients with COVID-19 decreased viral load at 11 days compared with placebo.

STUDY DESIGN: Randomized, double-blind, placebo-controlled, multisite single-dose trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFO: Preclinical studies of a neutralizing antibody for COVID-19 illness indicate that the treatment decreases respiratory tract viral loads. In nonhuman primates, LY-CoV555 has demonstrated passive protection against SARS-CoV-2. Authors report an interim analysis of phase II trial testing the antibody LY-CoV555.

PATIENTS: Recent COVID-19 diagnosis
INTERVENTION: Single-dose of LY-CoV555 of 700 mg, 2,800 mg, or 7,000 mg
CONTROL: Placebo
OUTCOME: Viral load at day 11

Secondary Outcomes: Safety, symptom burden, clinical outcome

METHODS BRIEF DESCRIPTION:

- Symptomatic COVID-19–positive patients were recruited from 41 outpatient centers in the United States.
  - Majority of patients had at least one risk factor for serious illness (≥65 years old, BMI ≥35 kg/m^2, or comorbid disease).
- 700 mg, 2,800 mg, or 7,000 mg of LY-CoV555 given intravenously over 1 hour compared with placebo.
- Primary outcome: Change in viral load from baseline to day 11.
- Secondary outcomes of patient symptoms, clinical outcomes, and safety were assessed through day 29 through a questionnaire and chart review.
- Repeated-measures analysis mixed model and treatment effects used.
- Sample size was determined by a model to simulate viral load.

INTERVENTION (# IN THE GROUP): 700 mg=101 patients; 2,800 mg=107 patients; 7,000 mg=101 patients
COMPARISON (# IN THE GROUP): 143

FOLLOW-UP PERIOD: 29 days

RESULTS:
Primary Outcomes:
- The log viral load decreased in all participants from baseline to 11 days.
  - Baseline mean=6.4 log viral load
  - Day 11 mean=2.6 log viral load
  - Mean difference (MD)=–3.8 log viral load (no measure of significance)
- All groups experienced a decline in the log viral load between baseline and day 11.
  - 700 mg=–3.7 log viral load
  - 2,800 mg=–4.0 log viral load
  - 7,000 mg=–3.4 log viral load
  - Placebo=–3.5 log viral load
- 2,800 mg of LY-CoV555 significantly reduced log viral load at 11 days compared with placebo (MD –0.53; 95% CI, –0.98 to –0.08).
- 700 mg and 7,000 mg of LY-CoV55 did not reduce viral loads significantly more than placebo:
  - 700 mg (MD –0.20; 95% CI, –0.66 to 0.25)
  - 7,000 mg (MD 0.09; 95% CI, –0.37 to 0.55)

Secondary Outcomes:
- Fewer patients in the treatment group were hospitalized compared to the placebo group (1.6% vs 6.3% respectively; no measure of significance).
- The treatment group experienced fewer symptoms compared with the placebo group:
  - Measured via symptom severity scores (0–3; 0=no symptoms: and 3=severe symptoms)
  - Day 4: MD –1.0 (95% CI, –1.6 to –0.49)
  - Day 11: MD –0.44 (95% CI, –1.0 to –0.15)
- Fewer patients in the treatment group reported adverse events compared with the placebo group (22.3% vs 24.5%, respectively; no measure of significance).
- Fewer patients in the treatment group reported serious adverse events compared with the placebo group (0% vs 0.7%, respectively; no measure of significance).

LIMITATIONS:
- Viral load has not been proven to be associated with symptom severity.
- There could be other effective doses.

- Privately funded by maker Eli Lilly, who developed the antibody.

EBP

Pebbles Shanley, MD
Elizabeth Clawson, DO
Janel Kam-Magruder, MD
Alaska Family Medicine Residency, Anchorage, Alaska

The authors declare no conflicts of interest.

Prescription opioid abuse: who is at risk?

Risk factors for misuse of prescribed opioids: a systematic review and meta-analysis

Cragg A, Hau JP, Woo SA, et al. Risk factors for misuse of prescribed opioids: a systemic review and meta-analysis. *Ann Emerg Med*. 2019; 74(5):634–646. DOI 10.1097/EBP.0000000000001149

KEY TAKEAWAY: Patients at higher risk of opioid misuse were younger, male, and reported a history of current substance use or mental health diagnoses.
STUDY DESIGN: Systematic review and meta-analysis of 65 observational and experimental studies: randomized control trials (n=1), cross-sectional (n=18), retrospective cross-sectional (n=4), prospective cohort (n=10), retrospective cohort (n=27), case-control studies (n=5)
LEVEL OF EVIDENCE: STEP 3.

BRIEF BACKGROUND INFORMATION: Increased opioid prescriptions and illicit use are implicated in the increase of opioid-related deaths. Despite this, opiates remain frequently prescribed, even if there are alternatives. Identifying high-risk patients of opioid misuse could prompt alternative prescribing and decrease opioid dependence/abuse

PATIENTS: Adults and children first exposed to opiates via prescription for noncancer or palliative care

INTERVENTION: Opiate tolerant Comparison: Opiate naive

OUTCOME: Opioid misuse (atypical drug behavior or aspect of predefined opioid addiction/dependence from ICD-10 or DSM-5).

METHODS (BRIEF DESCRIPTION): Systematic review of the literature per the Preferred Reporting Items for Systemic Reviews and Meta-analyses guidelines, and the Meta-analysis of Observational Studies in Epidemiology guidelines.

RESULTS: Sixty-five studies were included in the systematic review and 43 studies included in the meta-analysis (n=30,571,969–30,586,274). Pooled odds ratios on 27 dichotomous and six, continuous, commonly reported, opioid misuse risk factors were calculated. Sixteen dichotomous patient characteristics were associated with increased odds of opioid misuse including:

- Age <40 years (odds ratio [OR] 2.2; 95% CI, 1.8–2.6)
- Male sex (OR 1.2; 95% CI, 1.1–1.4).
- Previous opioid use/abuse (OR 3.8; 95% CI, 1.9–7.9)
- Current short-acting opioid use (OR 2.4; 95% CI, 1.2–5.0)
- Any illicit drug use history (OR 4.2; 95% CI, 2.3–7.6)
- Any mental health diagnoses (OR 2.5; 95% CI, 1.9–3.2).

Opioid dose was associated with opioid misuse (mean difference [MD] 81 MME/d; 95% CI, 39-124). However, opioid supply was not associated with opioid misuse (MD 147 days; 95% CI, -33 to 328).

LIMITATIONS:

- Study did not evaluate interactions between risk factors.
- Unable to account for residual confounding from observational studies.
- Significant heterogeneity in the included studies.
- Did not assess provider- or system-level risk factors. EBP

Danny Ebert, MD
Good Samaritan Hospital Medical Center
Corvallis, OR

The author declares no conflicts of interest.

Do current maternal glucose targets during labor affect neonatal outcomes?

CASE EXAMPLE

Jennifer is a 33-year-old G3P2 diagnosed with gestational diabetes mellitus at 26 weeks which is controlled with diet and exercise. She presents for induction of labor at 39 3/7 weeks. Her initial blood glucose level is 118 mg/dL. Should the patient be started on an insulin drip?

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Bottom line

One small randomized control trial (RCT) demonstrated a statistically significant decrease in neonatal blood glucose levels in the first 24 hours of life following tight (<100 mg/dL) as compared with more liberal (<120 mg/dL) glucose labor targets in women with gestational diabetes mellitus (GDM), but no difference in incidence of neonatal hypoglycemia below 40 mg/dL, treatment of neonatal hypoglycemia, or neonatal intensive care admission. One systematic review found no consistent correlation between intrapartum glucose measurements and neonatal hypoglycemia. No high-quality studies have looked at maternal-specific outcomes or involved scheduled cesarean section.

Review of the evidence

A 2019 RCT of 76 women assessed the effects of tight compared with liberalized intrapartum maternal glucose management on neonatal hypoglycemia in pregnancies complicated by GDM. Inclusion criteria were maternal age 18 years old or older, a diagnosis of GDM, singleton gestation without major fetal anomalies, and English or Spanish fluency. Patients with pregestational diabetes were excluded.[1] Patients were randomized at 36 weeks' gestation in a 1:1 ratio to either tight glucose control (target BG 70–100 mg/dL) or more liberalized control (70–120 mg/dL). In the tight control group, blood glucose levels were checked every hour. Treatment was initiated for single blood glucose >100 mg/dL or <60 mg/dL. In the liberalized control group, blood glucose was checked every four hours, with treatment initiated for a single maternal blood glucose level >120 mg/dL or <60 mg/dL. The primary and secondary outcomes included neonatal blood glucose measurements in the first 24 hours of life. No statistically significant difference was noted in mean first neonatal blood glucose between groups (53 mg/dL after tight control vs 58 mg/dL after liberalized control; 95% CI, –12.66 to 4.26, $P=.60$). However, mean glucose levels in the first 24 hours of life were significantly lower in the tight control group (54 vs 58 mg/dL; 95% CI, –7.07 to 0.29, $P=.049$). Mean birth weight did not differ between the two groups. None of the other secondary outcomes were statistically significant, including incidence of neonatal hypoglycemia (defined as <40 mg/dL), interventions for neonatal hypoglycemia, and neonatal intensive care admission.

A 2013 review of 19 studies on the management of intrapartum glucose in women with pregestational and gestational diabetes (N=1,996 women) concluded that a maternal intrapartum goal glucose range of 4.0 to 7.0 mmol/L (72–126 mg/dL) reduces the risk of neonatal hypoglycemia. Of the 19 reviewed studies, 10 showed an inverse relationship between maternal intrapartum glucose and neonatal glucose measurements, three showed a trend toward this relationship, and six studies showed no relationship.[2] This was not a meta-analysis and the authors did not clearly describe their methods or perform a quality assessment of the included studies.

A 2017 systematic review included 23 studies with a total of 2,835 women with pregestational or gestational diabetes. Six of the 23 studies showed a direct relationship between maternal hyperglycemia and neonatal hypoglycemia, five showed this relationship in some but not all analyses, and 12 showed no statistically significant relationship.[3] Only one study was considered at low risk of bias. The included studies did not consistently report or adjust for potential confounders including preterm delivery, infant size for gestational age, maternal body mass index, third trimester glucose control, intrapartum maternal hypoglycemia, and mode of delivery. A meta-analysis was not performed because of significant heterogeneity between studies.

Recommendations from others

The Society of Obstetricians and Gynaecologists of Canada,[4,5] the Royal College of Obstetricians and Gynaecologists[6] and the US Endocrine Society[7] all recommend that blood glucose levels should be maintained between 4 and 7 mmol/L (72–126 mg/dL) during labor to reduce

the rate of neonatal hypoglycemia. Diabetes Canada recommends that blood sugars remain <7 mmol/L (126 mg/DL) during labor. American College of Obstetricians and Gynecologists recommends keeping intrapartum blood glucose levels <110 mg/dL for women with pregestational diabetes mellitus[8] but makes no formal recommendations on the management of women with GDM.[9]

CASE FOLLOW-UP

Despite hospital protocol recommendation to initiate an insulin drip at maternal blood glucose above 110 mg/dL, the team defers treatment of the initial BG value of 118 mg/dL, citing other societal recommendations that allow for more liberalized intrapartum glucose management. Subsequent blood glucose levels checked every four hours range between 100 and 120 mg/dL. Jennifer has an uncomplicated normal spontaneous vaginal delivery of an appropriate for gestational age male neonate whose blood sugars are monitored per hospital protocol. The infant has an unremarkable newborn nursery course and is discharged home without complication. EBP

William Michael, MD
Alyssa Bruehlman, MD
Sarina Schrager, MD, MS
Department of Family Medicine and Community Health
University of Wisconsin
Madison, WI

The authors declare no conflicts of interest.

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In patients receiving androgens for gender dysphoria, is subcutaneous testosterone administration equivalent to IM administration?

EVIDENCE-BASED ANSWER

Perhaps. Subcutaneous (SQ) administration of testosterone results in similar serum levels of testosterone to IM=intramuscular administration (SOR: **C**, small cohort trial of disease-oriented evidence). Up to around 90% of patients previously on intramuscular, prefer SQ administration once switched over (SOR: **C**, cohort and case series).

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A 2018 prospective, open-label, crossover study examined the pharmacokinetics, safety, and patient acceptability of subcutaneous (SQ) versus IM=intramuscular testosterone injection for gender-affirming therapy.[1] Patients included were 14 transgender males (assigned sex at birth was female with a current gender identity of male) with a mean age of 30 years old on a stable dose of self-administered IM testosterone (30–110 mg weekly) for a minimum of eight weeks. Patients were cared for at a Canadian Gender Specialty Clinic and seven of the 14 had previously undergone hysterectomy-oophorectomy. Patients were treated with self-injected IM testosterone cypionate or enanthate for three weeks followed by SQ injections for eight weeks, using the same testosterone formulation and dosage previously used for IM administration. Trough serum testosterone concentrations were measured weekly and serial total serum testosterone measured on postinjection days one, three, and five and at weeks three and 11. Primary outcomes were total serum testosterone concentration and patient preference. No significant difference was noted in testosterone exposure for patients at week three with IM injections compared with week 11 with SQ injections (1.9 vs 1.7 nmol·d/L/mg, $P>.05$). In a final questionnaire, 13 of 14 patients (93%) preferred SQ versus IM injections, with one patient being unsure. No harms of SQ versus IM administration of testosterone were identified.

A 2017 retrospective case series (N=63) examined if SQ testosterone could be safely and effectively used as an alternative therapy to IM administration while consistently achieving serum testosterone concentrations within a normal range for an adult male.[2] A total of 63 transgender males who chose SQ injections and also completed all dose adjustments were included. Patients with abnormal hepatic or renal function, those with testosterone levels already above 50 ng/dL, and those on progesterone were excluded. Of the included patients, about 10% had a hysterectomy-oophorectomy before the start of the study and 35% had already been on IM treatment. Patients were started on an initial dose of 50 mg of SQ testosterone cypionate or enanthate weekly with adjustments made as needed to achieve serum testosterone concentrations within the normal cis adult male range. Testosterone levels were measured at baseline, day one, then 3 to 4 days after the fourth dose, once optimized then measured every six to 12 months. Patients were asked at each office visit about masculinization features such as absence of vaginal bleeding, facial hair changes, and deepening of voice. Primary outcomes were serum concentrations of free and total testosterone and total estradiol, masculinization, and clinical surveillance for reactions at injection sites. Serum testosterone levels within the normal cis adult male range was achieved in all 63 patients by the SQ route with the median dose at about 77 mg (range 50–150 mg). The study included 53 premenopausal patients, 51 (96%) achieved amenorrhea, and 35 (66%) achieved serum total estradiol concentrations less than 50 pg/mL, nine patients (17%) had levels from 50 to 54 pg/mL, and eight patients (15%) had levels greater than 54 pg/mL. All patients who received the optimized dose for at least six months reported deepening of the voice and the appearance of terminal facial hair. Of the patients who switched from IM to SQ (n=22), 91% indicated a marked preference for SQ. Minor and transient local reactions at the injection site were reported in nine of 63 patients. EBP

Amanda Kupris, MD
Timothy Ramer, MD
University of Minnesota Medical Center Family Medicine Program, Minneapolis, MN

The authors declare no conflict of interest.

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Is cannabidiol an effective treatment of anxiety in adults?

EVIDENCE-BASED ANSWER

Probably not. Cannabidiol (CBD) alone does not relieve anxiety in adults compared with placebo (SOR: **C**, meta-analysis of 2 small randomized controlled trial). There might be benefit in 18- to 19-year-old patients taking CBD for social anxiety disorder (SAD; SOR: **C**, small pre-post study).

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A 2019 meta-analysis (40 randomized controlled trials [RCTs], N=3,067; 43 observational studies; patient number not reported) investigated the effectiveness of cannabinoids for the treatment of psychiatric disorders in adults.[1] Patients were adults ≥18 years old with a psychiatric disorder (anxiety, depression, attention deficit and hyperactivity disorder, Tourette syndrome, and post-traumatic stress disorder). Two RCTs (N=44) specifically assessed CBD alone for the treatment of anxiety. Both RCTs examined patients with a diagnosis of SAD. Anxiety symptoms were evaluated using the self-reported Visual Analogue Mood Scale (VAMS; range 0–100, 100=maximum anxiety). One RCT (n=24; 50% male; mean age 23.6 years old) evaluated VAMS scores before, during, and after a simulated public speaking activity, while the other RCT (n=20; 100% male; mean age 24.2 years old) evaluated VAMS scores before and after treatment administration only. Participants were given a one-time dose of either CBD (400–600 mg dissolved in corn oil) or placebo (corn oil alone). CBD was no better than placebo in reducing anxiety (2 RCTs, N=44; standard mean difference [SMD] $=-0.87$; 95% CI, -2.0 to 0.27, $I^2=85\%$).

A 2019 double-blinded pre-post study (n=37) investigated the effectiveness of CBD for the treatment of SAD.[2] Patients were adult Japanese teenagers (18–19 years old; 70% male) with a diagnosis of SAD and persistent symptoms for at least six months. All were treatment-naive to cannabis. Exclusion criteria included previous or concurrent medication or psychological treatment for social anxiety, comorbid diagnosis of other anxiety disorder, mood disorder, personality disorder, suicidality, or drug or alcohol dependence. Patients received either 300 mg of oral CBD (intervention group) or placebo (control group) daily for four weeks. Changes in anxiety symptoms preintervention and postintervention were measured using two self-reported scales: the Fear of Negative Evaluation Questionnaire (FNE; range 0–30, higher score=higher social anxiety) and the Liebowitz Social Anxiety Scale (LSAS; range 0–100, higher score=more severe social anxiety). No difference was noted between initial FNE or LSAS scores between groups. The CBD group demonstrated improvement between preintervention and postintervention mean values for FNE (24.4 vs 19.1, respectively; $P=.02$) and LSAS (74.2 vs 62.1, respectively; $P=.03$), whereas the placebo group did not (FNE 23.5 vs 23.3, respectively; $P=.29$; LSAS 69.9 vs 66.8, respectively; $P=.42$). This study was limited by a lack of a comparison of the mean differences between groups and did not address adverse effects. EBP

Andrew N. Rouble, MD, MSc
Bachir Tazkarji, MD
Family Medicine Residency Program
University of Toronto, Mississauga
Ontario, Canada

The authors declare no conflicts of interest.

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Does podophyllin provide any benefit over cryotherapy for adult patients with genital warts?

EVIDENCE-BASED ANSWER

No. Cryotherapy with liquid nitrogen may be superior in clearing genital warts when directly compared to topical podophyllin treatments (SOR: **C,** small randomized controlled trial [RCT]). Podophyllin does not appear to provide any additional benefit in genital wart clearance when combined with cryotherapy (SOR: **C**, small RCT).

DOI 10.1097/EBP.0000000000001277

A 2019 randomized controlled trial (RCT; n=104) compared the efficacy and safety of podophyllin resin with cryotherapy in the treatment of anogenital warts.[1] Male and female patients 16 to 60 years old with clinically visible warts were included in the study. Patients who were pregnant or immunocompromised were excluded. Patients were randomly assigned to receive liquid nitrogen cryotherapy (n=52) or 25% podophyllin resin (n=25) for four weeks. Cryotherapy was administered for 10 seconds weekly, and podophyllin resin was applied topically with a cotton bud to the appropriate area twice weekly for four weeks under supervision. Follow-up for resolution and recurrence of warts was done eight weeks after the initiation of treatment. A 90% or greater clearance was graded as excellent, 60% to 89% was considered good clearance, 30% to 59% satisfactory, and <30% a poor response. At eight weeks, there was a significantly higher proportion of patients experiencing an excellent response to cryotherapy compared with those treated with podophyllin (88% vs 8%; $P<.001$), although the podophyllin group did achieve a relatively high percentage (73%) of a good response. No poor responses were found in either group.

A 2017 RCT (n=60) measured the effectiveness of liquid nitrogen cryotherapy alone or in combination with podophyllin application in the treatment of genital warts.[2] Male and female patients of 20 to 38 years old with multiple genital warts were recruited from single US STD clinic for inclusion. Pregnant, lactating, and immunocompromised patients were excluded from the study. Patients were randomized to receive either a double freeze thaw cycle (lesion sprayed for 25 seconds per cycle) of cryotherapy with liquid nitrogen or cryotherapy followed by 25% podophyllin in tincture benzoin solution applied with a cotton bud. Following either treatment, patients were given broad-spectrum antibiotics along with skin ointment to use twice daily until the wound was healed. If 30% or more of the original lesions were present at the four-week follow-up, the procedure was repeated. At 24 weeks of follow up, no significant difference was observed between patients receiving cryotherapy alone versus those receiving cryotherapy plus podophyllin in a complete response (76% vs 77%; $P=.16$) or in recurrence rates (30% vs 38%; $P=.25$). EBP

Cheryl K. Verma, MD
James Brecheisen, MD
Chase Helm, MD
University of AR Medical Sciences- Southwest Texarkana, AR

The authors declare no conflicts of interest.

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Do periodic health evaluations improve outcomes?

EVIDENCE-BASED ANSWER

The periodic health evaluation enhances delivery of certain preventive services. However, it has not been shown to reduce overall, cardiovascular, or cancer-related mortality (SOR: **B**, meta-analysis and systematic review of data before the year 2000).

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A 2012 systematic review and meta-analysis (14 randomized controlled trials [RCTs]; N=182,880) examined morbidity of adults who received periodic health evaluations (PHEs) compared with those who did not.[1] Patients were 18 years old or older without known risk factors for disease or known diseases (such as hypertension or diabetes) and were seen in primary care clinics. The researchers included trials that examined visits in which screening for more than one disease or risk factor in more than one organ system was performed. Screening visits occurred at least once with average frequency or number of visits not reported. Studies that focused exclusively on geriatric populations were excluded. The primary outcomes were total mortality and mortality resulting from cardiovascular disease and cancer. Length of follow-up varied from 1 to 22 years. No effect of PHEs was noted on total mortality (7 RCTs; N=155,899; risk ratio [RR] 0.99; 95% CI, 0.95–1.0, I^2=0%), cardiovascular mortality (8 RCTs; N=152,435; RR 1.0; 95% CI, 0.9–1.2, I^2=64%), or cancer mortality (8 RCTs, N=139,290; RR 1.0; 95% CI, 0.92–1.1, I^2=33%). This study was limited by the use of data from the 1960s

TABLE. Outcome effect size and overall impact of periodic health evaluations in data from the US and other western countries[2]

Outcome	Overall effect	GRADE rating	Studies	Study effect size[a]
Delivery of preventive services				
Papanicolaou smear	**Beneficial**	**High**	RCTs (2)	Small to large
Fecal occult blood testing	**Beneficial**	**High**	RCTs (2)	Large
Cholesterol screening	**Beneficial**	**Medium**	RCTs (1) Observational (4)	Small to large
Immunizations	Mixed	Medium	RCTs (3)	—
Mammography	Mixed	Low	RCTs (1) Observational (1)	—
Proximal outcomes				
Patient attitudes (worry)	**Beneficial**	Medium	RCTs (1)	—
Blood pressure control	Mixed	High	RCTs (2)	—
Health habits	Mixed	Medium	RCTs (5)	—
Disease detection	Mixed	Medium	RCTs (2)	—
BMI	Mixed	Medium	RCTs (3)	—
Distal outcomes				
Costs	Mixed	Medium	RCTs (4)	—
Disability	Mixed	Medium	RCTs (2)	—
Hospitalization	Mixed	High	RCTs (3)	—
Mortality	Mixed	Medium	RCTs (5)	—

[a] Cohen *d* effect size: small (≤0.25), intermediate (0.26–0.8), or large (>0.8). Not reported on all measures. —=not reported; GRADE=Grading of Recommendations, Assessment, Development, and Evaluation criteria (high rating=unlikely further research would alter conclusion; medium rating=further research could alter conclusion; low rating=likely that further research would alter conclusion).

through the 1990s and may not accurately represent modern PHE effectiveness.

A 2007 systematic review (10 RCTs; 23 observational studies; number of patients not reported) examined the benefits and harms of the PHE in regard to delivery of clinical preventive services (Papanicolaou smears, cholesterol screening, and colorectal cancer screening), patient proximal outcomes (disease detection, blood pressure, and cholesterol), and distal outcomes (costs, disability, hospitalization, and mortality).[2] Participants were 18 years old, with the majority of studies coming from the United States and other studies from the United Kingdom, Canada, Taiwan, Japan, Denmark, and Sweden. The studies ranged widely in practice settings. In this review, PHE was defined as one or more visits with a provider solely for assessing overall health and risk factors for preventable disease. Researchers investigated whether the PHE resulted in greater benefits or a reduction in harms compared with non-PHE visits. The magnitude of effect for each study was measured using a Cohen *d* effect size and labeled small (≤0.25), intermediate (0.26–0.8), or high (>0.8). Outcomes were identified as beneficial (all studies showed benefit), harmful (all studies showed harm), or mixed (mix of beneficial and harmful studies). Outcomes were also classified using the Grading of Recommendations, Assessment, Development, and Evaluation criteria (high rating=unlikely further research would alter conclusion; medium rating=further research could alter conclusion; low rating=likely that further research would alter conclusion) to establish strength of evidence. Only four outcomes (Papanicolaou smear, fecal occult blood testing, cholesterol screening, and patient attitude) demonstrated a beneficial overall effect, with all other outcomes demonstrating a mixed overall effect (see **TABLE**). This study was limited by reliance on data collected in the 1960s through the 1990s. The authors also noted the difficult inherent in isolating the PHE as the direct cause of the outcomes studied. EBP

K. Nesa Mohebpour, MD
Matthew A. Breeden, MD
Saint Louis University FMR
Saint Louis, MO

The authors declare no conflict of interest.

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Do probiotics provide symptom relief in patients with SIBO compared with placebo or no treatment?

EVIDENCE BASED ANSWER

Probably. Probiotics provide abdominal pain relief in adult patients with small intestinal bowel overgrowth but do not consistently reduce daily stool frequency (SOR: **C**, meta-analysis of small randomized controlled trials and cohorts, and a single prospective cohort study). A 2-month course of *Saccharomyces boulardii* can decrease rates of diarrhea, gas symptoms, and abdominal pain (SOR: **C**, small prospective cohort study).

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A 2015 meta-analysis (N=1,796) of 12 randomized controlled trials (RCTs), two cluster RCTs, four retrospective, and four prospective cohort studies assessed the effectiveness of probiotics for the treatment and prevention of small intestinal bowel overgrowth (SIBO).[1] Almost all of the patients were adults (95%), with a few studies including children as well (5%). Underlying conditions for patients other than SIBO included irritable bowel syndrome, liver disease, gastric and colorectal cancer, and chronic proton-pump inhibitor treatment. Probiotic strains and doses varied greatly among studies with treatment lasting from one to six weeks. Treatment regimens included *Lactobacillus casei* (dose range 24 million to 6.5 billion bacteria daily), *L casei* followed by rifaximin 400 mg daily, *L casei* 1.5 g daily plus *Lactobacillus acidophilus* 1.5 g daily, *L casei* plus *Lactobacillus fermentum* 30 billion bacteria daily plus *S boulardii* 1.5 g daily. Other probiotic regimens (doses not given) included

Bifidobacterium bifidum, *Bifidobacteria lactis*, *Bifidobacteria longum*, *Lactobacillus rhamnosus*, and *Streptococcus thermophilus*. Comparison groups received either placebo or short chain fructo-oligosaccharides 2.5 g daily followed by rifaximin 400 mg daily. Outcomes measured included abdominal pain levels and daily stool frequency. Results were pooled and converted into a weighted mean difference (WMD) due to heterogeneity among scoring scales used. Patients treated with probiotics experienced a significant decrease in abdominal pain levels compared with nonprobiotic groups (2 studies; N=54; WMD, –1.2; 95% CI, –2.3 to –0.04). However, the probiotic group did not experience a significant decrease in daily stool frequency compared with nonprobiotic groups (4 studies; N=89; WMD, –0.09; 95% CI, –0.07 to 0.29).

A 2018 open-label, prospective, cohort trial in Mexico (n=40) examined the effect of differing probiotic treatments on the eradication and symptom management of SIBO in patients with systemic sclerosis.[2] Patients (mean age, 53 years; 95% female) were diagnosed with SIBO via a positive hydrogen breath test and were included with normal white blood cell counts and a confirmed diagnosis of systemic sclerosis. Participants were randomized to either metronidazole 500 mg twice daily followed by *S boulardii* 200 mg twice daily (n=13), only metronidazole 500 mg twice daily (n=13), or only *S boulardii* 200 mg twice daily (n=14). Monotherapy groups received treatment for one week per month for two months, and the combination group received therapy for two weeks per month for two months total. Eight gastrointestinal symptoms (reflux, disrupted swallowing, diarrhea, incontinence, nausea and vomiting, constipation, abdominal pain, gas/bloating/flatulence) were evaluated using the National Institutes of Health Patient-Reported Outcomes Measurement Information System in Gastrointestinal Symptoms (NIH-PROMIS GI). Each symptom subscale has a raw score (0-51) quantifying severity as asymptomatic, minimal, mild, moderate, and severe. Higher NIH-PROMIS GI scores denote greater severity in symptoms. Symptoms were assessed at baseline and after completion of the intervention. Compared with baseline, the probiotic only group experienced significant improvement in reflux (21 vs 14; *P*=.004), disrupted swallowing (10.5 vs 8; *P*=.01), diarrhea (8.5 vs 7.5; *P*=.05), fecal incontinence (6 vs 4; *P*=.04), abdominal pain (7 vs 6; *P*=.05), and gas/bloating/flatulence (22.5 vs 17.5; *P*=.01). The probiotic and metronidazole combination group experienced significant decreases in only abdominal pain (9.5 vs 5.5; *P*=.02) and gas/bloating (26 vs 13; *P*=.01). The metronidazole only group did not have any significant decreases in symptoms. EBP

Kristel Chatellier, PharmD, BCPS
Leah Stem, MD, MS
Patricia Klatt, PharmD, BCPS
Amy Haugh, MLS
Gretchen Shelesky, MD, MS
UPMC St. Margaret, Pittsburgh, PA

The authors declare no conflicts of interest.

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Is iron therapy effective in treating restless leg syndrome?

EVIDENCE-BASED ANSWER

Yes. Iron therapy moderately reduces restless leg syndrome (RLS) severity compared with placebo with similar rates of adverse events (SOR: **A**, meta-analysis of randomized controlled trials). Intravenous ferric carboxymaltose is recommended as a first-line treatment of moderate-to-severe RLS in patients with serum ferritin <300 μg/L and transferrin <45% concentration. Oral ferrous sulfate 325 mg twice daily should be considered in patients with serum ferritin <75 μg/L (SOR: **C**, expert opinion).

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A 2019 meta-analysis of 10 randomized controlled trials (RCTs; N=428) evaluated the efficacy of iron therapy in reducing severity of restless leg syndrome

(RLS).[1] Patients were adults who had symptomatic RLS diagnosed by expert interview or International Restless Legs Syndrome Study Group (IRLSSG) criteria. The experimental group received iron treatment either intravenously (ferric carboxymaltose [FCM], iron sucrose, or iron dextran for a total of 1,000 mg) or orally (ferrous sulfate 325 mg twice a day for 12 weeks), and the control groups received placebo or pramipexole (1 study). Most studies used the International Restless Legs Scale (IRLS) to evaluate improvement in RLS symptoms (a 40-point scale, with higher scores indicating severe symptoms). The primary outcome was restlessness or unpleasant leg sensation, and secondary outcomes included quality of life. Iron treatment resulted in moderate improvement in RLS symptoms compared with placebo groups during follow-up assessments at 2 to 14 weeks (8 studies; N=370; standardized mean difference [SMD] –0.74; 95% CI, –1.26 to –0.23). No difference was noted between iron and pramipexole in RLS symptoms using the IRLS (1 study; n=30; MD –0.4; 95% CI, –5.9 to 5.1). Iron treatment groups had improved quality of life in studies using a continuous measure (3 studies; N=128; SMD 0.51; 95% CI, 0.15–0.87; I^2=0%), whereas no difference was observed in studies using a dichotomized measure (2 studies; N=39; risk ratio [RR] 2; 95% CI, 0.54–7.45; I^2= 54%). Dropout rates because of treatment inefficacy and adverse events such as gastrointestinal symptoms were not different between treatment and placebo groups (9 studies; N=391; RR 0.77; 95% CI, 0.41–1.5; I^2=43%; and 6 studies; N=298; RR 1.5; CI, 0.97–2.3). Pramipexole treatment was associated with more adverse events than iron therapy (1 study; no data provided). Limitations of this meta-analysis included high heterogeneity, lack of blindness, and high dropout rates in some studies.

A 2018 clinical practice guideline by an IRLSSG task force underwent systematic review of 31 articles (the 10 RCTs from above included) to evaluate efficacy of different types of iron formulation in reducing severity of RLS.[2] The IRLSSG recommended FCM 500 to 1,000 mg intravenous as a first-line treatment. The IRLSSG stated FCM is effective in reducing moderate to severe RLS symptoms at 4 to 6 weeks in nonanemic patients with serum ferritin level <300 μg/L and transferrin saturation <45% (level A recommendation, based on 3 high-quality and 3 low-quality studies). The panel also recommended oral ferrous sulfate 325 mg (65 mg elemental iron) twice a day with vitamin C 100 mg twice daily as a treatment of RLS when the serum ferritin level is ≤75 μg/L. The task force stated that oral iron may not be effective for the treatment RLS in adults who have serum ferritin >75 μg/L (level C recommendation, based on low-quality studies). Iron sucrose was considered not effective based on one study, and the efficacy of other formulations, including iron dextran, iron gluconate, feruomoxyol, and isomaltoside, were deemed inconclusive because of inadequate information. EBP

Grace Yoon, MD
Carol J. Howard, MD
In His Image Family Medicine Residency Program
Tulsa, OK

The authors declare no conflicts of interest.

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Is there an effective way to adjust statin type, dosing, and/or frequency to maximize cardiovascular risk benefit and simultaneously eliminate muscle aches in patients who experience that side-effect?

EVIDENCE-BASED ANSWER

Perhaps. Alternate-day dosing with long half-life statins atorvastatin and rosuvastatin are as effective as daily dosing in reducing LDL levels (SOR: **C**, disease-oriented outcomes from a meta-analysis of randomized controlled trials [RCTs]). Switching to alternate-day rosuvastatin dosing may improve symptoms in up to 73% of patients previously intolerant due to myalgias (SOR: **C**, 1 low-quality RCT and 1 retrospective analysis).

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A 2017 meta-analysis of 12 randomized controlled trials (RCTs) and one quasi-RCT (N=1,023) assessed the efficacy of alternate day versus daily dosing of statins in patients.[1] Participants were 64% male with a mean age of 56 years, and baseline LDL of 142 mg/dL (range, 78–190 mg/dL). All studies compared the efficacy of alternate-day dosing of statin therapy versus daily dosing on one or more lipid parameters (total cholesterol, LDL, triglycerides) for a duration of greater than six weeks (range, 6–24 weeks) and reported complete lipid panels following treatment. Included statins were atorvastatin 10 to 20 mg daily versus 10 to 20 mg every other day (8 trials;) and rosuvastatin 10 mg daily versus 10 to 20 mg every other day (3 trials). No significant reduction in LDL levels was observed between patients in the daily group compared with the every other day group for both atorvastatin (8 trials; N=331; mean difference [MD], 6.8 mg/dL; 95% CI, –1.6 to 15 mg/dL; I^2=81%) and for rosuvastatin (3 trials; N=196; MD 10.5 mg/dL; 95% CI, –0.23 to 21 mg/dL; I^2=69%). In this same analysis, pravastatin and fluvastatin, satins with shorter half-lives, were found to be less effective with alternate-day dosing.

A 2011 randomized, double-blind, placebo-controlled crossover study assessed 17 Milwaukee Veterans Affairs (VA) patients with hyperlipidemia.[2] Included patients had a history of statin myalgias without significant baseline CPK elevations (greater than 1,000 units/mL) and not at an acceptable LDL goal. Patients were adult men with a mean age of 65 years, mean BMI of 31 kg/m^2, and a mean baseline LDL of 142 mg/dL. Any patient with an adverse reaction other than myalgias, or patients with at-goal LDL levels based on last reading were excluded. Differences in LDL reduction and tolerability from baseline between rosuvastatin and placebo groups were evaluated as the primary outcome. Secondary outcomes included the difference in percentage of patients tolerating rosuvastatin and placebo during each treatment period. Patients were randomized through two separate, eight-week treatment phases receiving either rosuvastatin 5 mg once weekly or placebo. If not at LDL goal at week four, the dose was increased to 10 mg once weekly. The once-weekly rosuvastatin group significantly reduced LDL levels compared with placebo (–12% vs 0.4%; *P*=.002). There were similar rates of myalgias between the rosuvastatin group (20%) and the placebo group (12%) (no *P value* available).

A 2008 retrospective analysis of 51 patients with statin intolerance from two separate lipid clinics in the United States evaluated the effect and tolerance of alternate-day rosuvastatin therapy.[3] Patients were included for analysis if they had documented statin intolerance, received alternate-day rosuvastatin for at least one month, and had lipid panel reports from before and after alternate-day treatment. Those included were mostly (55%) female, had a mean age of 59 years, and had myalgias (77%) and increased transaminase levels (20%) as the most common manifestations of prior statin intolerance. Patients who reported nonadherence to any lipid-altering agent during the observation period were excluded from the study. Patients received a mean dose of 5.6 mg of rosuvastatin on alternate-day dosing (range, 2.5–10 mg) for an average of four months. Intolerance was measured and collected via patient feedback. Overall, tolerance was observed in 73% of all patients. Of those who reported intolerance (n=14), myalgias was the most common reason (10 of 14). Additionally, patients who tolerated treatment significantly reduced LDL levels at follow-up compared with baseline (mean reduction –35%; *P*<.001). EBP

Nolan R. Schmitz, PharmD, BCPS
Archana Raghavan, PharmD, BCPS
Amy Haugh, MLS
Suzan Skef, MD, MS
UPMC St. Margaret FMRP, Pittsburgh, PA

The authors declare no conflicts of interest.

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Are multimedia educational interventions more effective than conventional education at reducing HbA1c in adults with type 2 diabetes?

EVIDENCE-BASED ANSWER

Multimedia educational interventions that interact with users to generate tailored content reduce HbA1c by 0.2% compared with conventional education (SOR: **A**, 1 systematic review with meta-analysis). Mobile phone application interventions have the largest effect, reducing HbA1c 0.5% compared with conventional education (SOR: **A**, 1 systematic review with meta-analysis). Among medically underserved adults, multimedia educational interventions performed similarly, reducing HbA1c by 0.27% (SOR: **A**, 1 systematic review with meta-analysis).

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A 2013 meta-analysis of 16 randomized controlled trials (RCTs; N=3,578) compared interactive computer-based diabetes self-management with tailored content to conventional education.[1] The study included adults 18 years old or older with type 2 diabetes (mean ages 46–67 years old and mean HbA1c 7.4–9.5%). The intervention comprised any computer technology application that facilitated one or more aspects of diabetes self-management through feedback, tailored advice, reinforcement and rewards, patient decision support, goal setting, or reminders. Examples included computer-based education sessions, online education in a peer forum, and a mobile phone-based software coach that delivered tailored automated messages. The frequency of the intervention varied between once during the study up to two interactions per day. The study periods ranged from four weeks to 12 months. The control groups varied, including standard diabetes care, noninteractive computer-based programs, paper educational material, delayed start/waiting list, and face-to-face self-management education. Primary outcomes included the mean difference in HbA1c preintervention and postintervention. Compared with standard diabetes care, computer-based diabetes self-management interventions modestly improved HbA1c (11 trials; N=2,637; mean difference [MD] –0.2%; 95% CI, –0.4 to –0.1). A subgroup analysis showed a greater effect for mobile phone applications (3 trials; N=280; MD –0.5%; 95% CI, –0.7 to –0.3). No significant adverse events were noted. This meta-analysis was limited by trials not being double-blinded.

A 2017 meta-analysis of 13 RCTs (N=3,257) compared diabetes self-management education with health information technology compared with usual care in medically underserved adults.[2] Patients were 19 years old or older with type 1 or 2 diabetes (mean age 55 years old, 66% female, 74% ethnic minorities, and baseline HbA1c 7.1%–9.8%). Studies defined "medically underserved" as greater than 50% of the sample meeting federal poverty guidelines, being a member of a racial/ethnic minority, or residing in a rural area. The diabetes self-management intervention addressed at least one American Association of Diabetes Educators self-care behavior using a variety of health information technologies: telephone messaging or calls, internet-based applications, telehealth with messaging between patients and providers, and noninternet computer programs. Frequency and amount of interaction with the intervention varied from as little as two mandated interactions over six months to weekly interactions for 39 weeks. In many of the studies, the participants determined the amount of interaction with the intervention. The control group received usual care only, which included in-person education sessions, paper educational materials, and usual care plus diabetes quizzes. Primary outcomes included the mean difference in HbA1c preintervention and postintervention and its change at six or 12 months. The use of health information technology modestly improved HbA1c at six months (6 trials; N=1,055; MD –0.36%; 95% CI, –0.53 to –0.19) and at 12 months (6 trials; N=2,112; MD –0.27%; 95% CI, –0.49 to –0.04). No significant harms were observed. Limitations included a high risk of bias in many studies with control groups receiving only usual care and less overall diabetes education than the intervention subjects. This study used two of the same studies as the previously described 2013 systematic review with an overlap of 924 participants between the two systematic reviews. EBP

Stephen Cagle, MD
Andrew Lyell, MD
Southwest Illinois Family Medicine Residency
O'Fallon, IL

The authors declare no conflicts of interest.
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In patients with uncontrolled diabetes, does self-titration of insulin lead to faster glucose control compared with clinician-led instruction?

EVIDENCE-BASED ANSWER

No. Self-titration of insulin does not lead to faster glucose control compared with clinician-led instruction from 12 to 20 weeks of titration (SOR: **A**, consistent results from 2 randomized controlled trials).

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A 2017 Canadian open-label, randomized, multicenter, descriptive pilot study (n=212) examined the safety and efficacy of two different titration algorithms for treatment in patients with diabetes.[1] Patients were adults with uncontrolled type 2 diabetes who used basal insulin plus or minus noninsulin antihyperglycemic agents and whose HbA1c was greater than 7% but less than or equal to 10%. The studies also included uncontrolled diabetic patients who used noninsulin antihyperglycemic agents whose HbA1c was greater than 7% but less than or equal to 11%. Patients were excluded if using insulin other than basal. In the self-titrated group (n=108), patients self-titrated their insulin dosage by one unit per day until fasting self-monitored blood glucose (FSMBG) reached in the range of 4.4 to 5.6 mmol/L. In the clinician instructed group (n=104), the insulin dose was adjusted by the investigator based on the median FSMBG values of the last three days at least once weekly. Insulin treatment for both groups was long-acting glargine. The primary outcome was the percentage of subjects reaching FSMBG ≤5.6 mmol/L without nocturnal hypoglycemia or percentage of participants whose HbA1c was less than or equal to 7% at week 12. The secondary outcome was overall treatment satisfaction that was assessed by using the Diabetes Treatment Satisfaction Questionnaire and health care professional satisfaction questionnaire. After 12 weeks, no significant difference was observed in the proportion of patients in the self-titrated group compared with the clinician-led group for achievement of the goal FSMBG (19% vs 18%, $P>.05$) or in reaching an HbA1c of 7% or less (29% vs 27%, $P>.05$). The incidence of hypoglycemia and scores on the Diabetes Treatment Satisfaction Questionnaire were similar in both groups.

A 2017 20-week, open-label, randomized, two-armed, parallel group multicenter study (n=155) examined the efficacy of patient-driven versus physician-driven titration of 70/30 premix insulin (BIAsp 30) for glycemic control in patients not controlled on neutral protamine Hagedorn (NPH) insulin.[2] Patients were recruited from Egypt, Indonesia, Morocco, Saudi Arabia, and Vietnam. Adults included had a mean age of 55 years old and diagnosed with type 2 diabetes for at least 12 months before screening. Patients had been treated with NPH insulin for at least three months with a stable total daily dose of at least 1,500 mg or highest tolerable dose of metformin for at least two months. Inclusion criteria mandated an HbA1c of 7% to 10% and have a body mass index of less than or equal to 40 kg/m^2. Patients were randomly assigned 1:1 to receive patient-driven (n=69) versus physician-driven (n=68) titration of BIAsp 30 twice daily. BIAsp 30 was started at their previous insulin dose split into two equal doses before breakfast and

dinner. The dose was adjusted based on lowest finger stick glucose from previous three days. Doses were adjusted once a week during the training and every second week in the maintenance period. Patient-driven arm was seen in clinic three times at weeks four, 12, and 20 with telephone contact when deemed necessary. Physician-driven patients were seen six times at weeks two, four, eight, 12, 16, and 20 with phone call one week after their visit and when deemed necessary. After 20 weeks of treatment, no significant difference was noted in HbA1c lowering between those in the patient-driven titration group compared with the physician-driven group (mean difference –0.23%; 95% CI, –0.54% to 0.08%). EBP

Justin Teubert, DO
Christopher Kim, MD
Seth O'Neal, DO
United Hospital Center Family Medicine Program
Bridgeport, WV

The authors declare no conflicts of interest.

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Are continuous insulin pumps more effective than multiple daily insulin injections in the management of poorly controlled type 2 diabetes?

EVIDENCE-BASED ANSWER

Probably not. Although both continuous subcutaneous insulin infusion and multiple daily insulin injections were found to be effective at lowering HbA1c in patients with type 2 diabetes, conflicting evidence is present that fails to demonstrate one method is superior to the other (SOR: **C**, mixed evidence on disease-oriented outcomes in 3 randomized controlled trials).

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A 2014 multinational, six-month, nonblinded randomized controlled trial (RCT; n=331) compared the effectiveness of continuous subcutaneous insulin infusion with multiple daily insulin injections at lowering HbA1c in patients with poorly controlled type 2 diabetes.[1] Patients included were almost exclusively White and had a mean age of 56 years old. Baseline A1c levels for participants was around 9.0%. Patients were randomly assigned to either pump treatment rapid-acting insulin analogues (lispro, aspart, or glulisine) via continuous infusion (n=168) or both long-acting analogues (glargine or detemir) and the aforementioned short-acting analogues on a basal-bolus regimen of subcutaneous injections (n=163). After six months, patients in the continuous infusion group experienced a significantly greater decrease in A1c levels compared with those in the multiple injection group (mean difference –0.7%; 95% CI, –0.4% to –0.9%). Daily insulin use was also higher in the multiple injection group (122 vs 97 units, $P<.01$).Hyperglycemic and hypoglycemic events were infrequent and no difference was noted in the rate of diabetes-related adverse events in either treatment group. A limitation of the study was the exclusion of patients with daily insulin doses of more than 220 units.

A 2014 single-center, 12-week RCT (n=200) examined the efficacy of continuous subcutaneous insulin infusion or multiple daily insulin injections in a convenience sample of hospitalized adults with type 2 diabetes.[2] Patients included were Chinese, majority male, had a mean age of 51 years old, and demonstrated poor glycemic control. The continuous insulin group was treated with pre-prandial and basal insulin aspart via insulin infusion pumps while the multiple injection group was treated with pre-prandial bolus

insulin aspart and basal insulin glargine via subcutaneous injections for 12 weeks total. At 12 weeks, no noted difference was found in A1c reduction between the continuous pump group and the multiple injection patients (–3.8% vs –3.5%, *P*=.28). Severe hypoglycemic episodes (blood glucose of 3.9 mmol/L or less) did not occur in either treatment group.

A 2005 two-center, 12-month RCT (n=107) investigated the performance of continuous insulin infusions or multiple daily insulin injections in the treatment of patients with type 2 diabetes.[3] Included patients had a mean age of 60 years old and all had a HbA1c level of 7.0% or higher. Participants in the continuous insulin pump group were treated with preprandial and basal insulin lispro via insulin infusion pumps, whereas those in multiple injection group were treated with preprandial insulin lispro and once-daily insulin glargine via subcutaneous injection. After 12 months, no significant difference was noted in HbA1c reductions between patients treated in the continuous pump group compared with those in the multiple daily injection group (–1.7% vs –1.6%, *P*=.2). No differences were noted in severe hypoglycemic events between the two study groups; however, a single catastrophic hypoglycemic event was noted in the multiple injection group (the episode was associated with a motor vehicle crash after which the participant was hospitalized and recovered completely). EBP

Kristen A. Marotta, MD
David Etienne, MD
S. Sutton Hamilton, MD
Inspira Family Medicine Residency, Woodbury, NJ

The authors declare no conflict of interest.

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Does monitoring for albuminuria improve patient-oriented outcomes in patients with type 2 diabetes?

EVIDENCE-BASED ANSWER

Maybe. Intensively treating for microalbuminuria in type 2 diabetic patients does not reduce myocardial infarctions or mortality (SOR: **B**, low-quality meta-analysis), but patients with macroalbuminuria do experience higher rates of cardiovascular-related hospitalizations and mortality compared with those with normal levels of albuminuria (SOR: **B**, single large cohort study). Screening for abnormal levels of albuminuria is recommended to enable timely diagnose of chronic kidney disease and any risk complications (SOR: **C**, evidence-based practice guideline).

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A 2018 meta-analysis of seven randomized controlled trials (RCTs) examined intensive interventions to control blood pressures (BPs), HbA1c, and lipid levels in patients with type 2 diabetes and microalbuminuria.[1] Patients were mostly middle-aged, male, and had a diabetes onset before inclusion into a trial of 3 to 9 years with a confirmed diagnosis of microalbuminuria. Intensive control was defined as multifactorial interventions geared toward driving blood glucose, BP, and lipid levels down through lifestyle changes, behavioral modifications, and pharmacological interventions. Control groups received no increased interventions and usual standards of care. Patient outcomes measured were reduction in myocardial infarction, nonfatal strokes, cardiovascular events and all-cause mortality. After pooling the trials, no significant difference of intensive care versus standard care was noted in reduction of myocardial infarction (3 trials; N=784; risk ratio [RR] 0.50; 95% CI, 0.20–1.22),

reduction in nonfatal strokes (3 trials; N=784; RR 0.40; 95% CI, 0.10–1.91), reduction of cardiovascular mortality (3 trials; N=784; RR 0.95; 95% CI, 0.48–1.86), or reduction of all-cause mortality (3 trials; N=785; RR 0.80; 95% CI, 0.51–1.25). The author noted that the scope of the study was heavily influenced by one small trail, thus limiting the validity of the results.

A 2018 longitudinal cohort study (n=16,678) investigated the relationship between estimated glomerular filtration rate (eGFR), albuminuria, and risk of cardiovascular and all-cause mortality in patients with type 2 diabetes.[2] Patients had a mean age of 60 years old, 47% female, and the majority had a duration of diabetes around 12 years. Patients were categorized by their baseline eGFR, which was calculated by serum creatinine according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Patients were further characterized by their Kidney Disease Improving Global Outcomes categories for eGFR and their degree of albuminuria by urine albumin to creatinine ratio categories. Cardiovascular disease hospitalizations occurred at a significantly higher rate in patients with macroalbuminuria compared with patients with normal albuminuria or microalbuminuria (18% vs 8.2% and 14% per 1,000 person-years, $P<.5$). The rate of all-cause mortality also occurred at a significantly higher rate in patients with macroalbuminuria compared with patients with normal albuminuria or microalbuminuria (39% vs 14% and 26% per 1,000 person-years, $P<.05$).

A 2019 evidence-based clinical practice guideline from the American Diabetes Association recommended annual screening by assessing urinary albumin and eGFR in all patients with type 2 diabetes (level B: moderate supportive evidence from cohorts).[3] The guideline advocated for surveillance of albuminuria and eGFR to enable timely diagnosis of CKD, monitor progression of CKD, detect superimposed kidney diseases including acute kidney injury, assess risk complications, dose drugs appropriately, and determine whether nephrology referral is needed. EBP

Bethany Norberg, MD
Joe Asher, MD
Robert Wallette, MD
Ben Zeichner, MD
John Peter Smith Family Medicine Residency
Fort Worth, TX

The authors declare no conflicts of interest.

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Is there a mortality benefit in patients with COPD who take statins compared with those who do not?

EVIDENCE-BASED ANSWER

Probably. In patients with COPD, statins may reduce all-cause mortality and fatal acute COPD exacerbations (SOR: **B**, meta-analysis of randomized controlled trials [RCTs] and cohorts). Evidence on the use of simvastatin 40 mg is mixed on any provided benefit for all-cause mortality (SOR: **C**, conflicting evidence from a meta-analysis of RCTs and cohorts and a single RCT).

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A 2019 meta-analysis of 37 randomized controlled trial (RCTs) and 16 cohort studies (N=232,569) assessed the role of statins in reducing all-cause and cause-specific mortality in COPD patients.[1] The majority of studies recruited standard COPD patients, with about 1-third recruiting COPD patients who also had pulmonary hypertension. Treatment duration varied from 1 to 120 months, with studies mainly falling

between three and 12 months of treatment. Medications included atorvastatin 20 to 40 mg (12 studies), simvastatin 20 to 40 mg (13 studies), rosuvastatin 10 to 20 mg daily (4 studies), fluvastatin 20 to 40 mg (3 studies), pravastatin 40 mg (2 studies), and unspecified (16 studies). Studies looked at all-cause mortality, fatal acute exacerbations of COPD, and heart disease–related mortality. Patients treated with statins had significantly lower risk for all-cause mortality (13 studies; n=138,261; risk ratio [RR], 0.71; 95% CI, 0.62–0.80; I^2=67%) and fatal acute COPD exacerbations (10 studies; n=32,829; RR, 0.84; 95% CI, 0.79–0.89) compared with placebo. However, statins did not reduce heart disease–related mortality (3 studies; n=2,454; RR, 0.92; 95% CI, 0.83–1.03; I^2=55%) compared with placebo. Limitations included a lack of reported demographics, lack of statin type, or lack of doses for many studies, and only two RCTs included in the all-cause mortality analysis.

A 2014 multicenter, randomized, parallel-group, placebo-controlled trial (n=885) evaluated the effect of simvastatin 40 mg versus placebo for the prevention of COPD exacerbations.[2] Patients were between 40 and 80 years old with moderate-to-severe COPD, defined according to the Global Initiative for Chronic Obstructive Lung Disease criteria. All patients (mean age, 62 years) were former or current smokers, with a lifetime smoking of 10 pack-years or more, who also met at least one of the following criteria within one year prior to enrollment: use of supplemental oxygen, receipt of systemic glucocorticoids or antibiotic agents for respiratory problems, or presentation to the emergency department or hospitalization for COPD exacerbation. Patients were excluded if they were already receiving statins or should have been receiving statins according to established guidelines, and/or had a medical history of diabetes, active liver disease, and alcoholism. Patients were randomized to simvastatin 40 mg daily (n=430) or placebo (n=447) and followed for 12 to 36 months. Outcomes included all-cause and cause-specific mortality. No significant differences were found between the two groups with respect to any characteristics at baseline, including lipid levels. Simvastatin compared with placebo did not reduce all-cause mortality (6.5% vs 6.7%; *P*=.89) or cause-specific fatal events, such as rates of acute exacerbation of COPD (1.4% vs 1.1%; *P*=.72) and cardiovascular events (0% vs 0.2%; *P*=.33). EBP

Amisha P. Mehta, PharmD
Kevin Wissman, PharmD
Amy J. DiPlacido, MD, CWSP
UPMC St. Margaret, Pittsburgh, PA

The authors declare no conflicts of interest.

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In patients with COPD, does SMT improve lung function compared with no SMT?

EVIDENCE-BASED ANSWER

Maybe. Spinal manipulative therapy (SMT) seems to improve six-minute walk test and forced vital capacity in patients with chronic obstructive pulmonary disease compared with pulmonary rehabilitation or soft tissue techniques alone (SOR: **C**, 2 small unblinded randomized controlled trials [RCTs]). SMT can also improve patient-reported dyspnea scores, but this improvement is of questionable clinical significance (SOR: **C**, small unblinded RCT).

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A 2016 randomized controlled trial (RCT; n=33) examined the effect of spinal manipulative therapy (SMT) on pulmonary function in patients with a history of chronic obstructive pulmonary disease (COPD).[1] Patients (mean age 66 years old) were mostly female, from Australia, and referred for treatment by a respiratory specialist. Patients were excluded with extreme bone mineral density values if they had used tobacco in the last 12 months or were unable to complete a functional assessment. Participants were randomized into standard pulmonary rehabilitation, soft tissue treatment with pulmonary rehabilitation, or spinal

manipulation, soft tissue treatment, and pulmonary rehabilitation. Assessors were blinded to treatment groups; analysis was done as intention to treat. Pulmonary rehabilitation began with an eight-week introductory stage to assess capacity, followed by an eight-week maintenance stage, and ended with an eight-week nonintervention stage (exercise at own discretion). Soft tissue treatment was gentle effleurage, friction, and cross-fiber friction massage to posterior chest muscles for 20 minutes. Spinal manipulation was high-velocity, low-amplitude manipulation to thoracic intervertebral, costovertebral, and costotransverse joints. Soft tissue and spinal manipulation were done twice a week for eight weeks from week 4 to 12 of pulmonary rehabilitation by a single experienced practitioner. Patients in the combination of all three treatments had a significantly higher forced vital capacity (FVC) versus pulmonary rehabilitation alone (mean difference [MD] 0.40 L; 98% CI, 0.02–0.79 L) at 24 weeks, as well as significantly better six-minute walk test scores compared with the soft tissue with pulmonary rehabilitation group (MD 48 m; 98% CI, 8.9–88 m) at 24 weeks (MD 58 m; 98% CI, 4.7–112 m). The study was not blinded.

A 2013 RCT (n=15) of patients diagnosed with moderate COPD by a respiratory specialist compared functional status and pulmonary function testing before and after four weeks of treatment.[2] Majority of the patients were White males and had a mean age of 56 years old. Exclusion criteria were similar to study above as well as those with mild or severe COPD. Participants were randomized into soft tissue treatment (same protocol as above), soft tissue plus spinal manipulation (same protocol as above), or soft tissue plus spinal manipulation with continuous exercise (walking for 6 minutes). Each session lasted 15 to 30 minutes. Outcomes measured included changes in forced expiratory volume in 1 second (FEV1), FVC, six-minute walk test, and Chronic Respiratory Questionnaire Self-Administered Standardized (20 items; 4 domains: dyspnea, fatigue, emotional, mastery; each on 1–7 Likert scale; lower scores have more disability). No changes were seen in FEV1 between groups. A combination of all three treatments improved FVC at four weeks versus soft tissue alone (MD 1.01 L; $P<.001$) and soft tissue plus spinal manipulation (MD 1.00 L; $P<.001$). Distance on the six-minute walk test was significantly higher after a combination of all three treatments versus soft tissue alone (MD 168 m; $P<.001$) and soft tissue and spinal manipulation (MD 48 m; $P=.03$). Scores on the dyspnea domain of the respiratory questionnaire were higher (less disability) in combination treatment versus soft tissue alone (MD 0.44; $P<.001$) and in soft tissue and spinal manipulation versus soft tissue alone (MD 0.64; $P=.01$). EBP

Scott Brown, DO
Anne Williams, PharmD
Amy Haugh, MLS
Jeffrey Lineman, DO
Gretchen Shelesky, MD, MS
UPMC St. Margaret, Pittsburgh, PA

The authors declare no conflicts of interest.

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Do statins prevent sudden cardiac death in people with congestive heart disease without coronary artery disease?

EVIDENCE-BASED ANSWER

There is a lack of evidence specifically evaluating statin use for prevention of sudden cardiac death in nonischemic patients only. However, patients with reduced ejection fraction who were majority nonischemic did not experience lower incidence of sudden cardiac death when treated with statins (SOR: **C**, secondary outcomes from randomized controlled trial and prospective cohort).

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A 2008 multicenter, double-blinded randomized controlled trial (n=4,574) examined the effectiveness of rosuvastatin in treating patients with chronic heart failure.[1] Patients (mean age 68 years old, 77% male) were recruited from 357 clinics in Italy with ischemic (39%) and

nonischemic (60%) heart failure, ejection fraction of 40% or less, New York Heart Association (NYHA) class II to IV, or one hospital admission for congestive heart failure in the preceding year. Patients were excluded for non-cardiac comorbidity incompatible with sufficiently long follow-up, recent acute coronary syndrome or re-vascularization, planned upcoming cardiac surgery, or significant liver disease. Patients were randomized to receive either rosuvastatin 10 mg daily (n=2,285) or placebo (n=2,289) and were followed for a median of 3.9 years. The primary outcome was time to death or hospital admission because of cardiac reasons. Sudden cardiac death was evaluated as a secondary endpoint. Results were adjusted for time to death, admission for cardiovascular conditions, and use of angiotensin receptor blockers. After adjustment, no significant differences were noted in the rate of sudden cardiac death for those treated with rosuvastatin and those in the placebo group (adjusted hazard ratio [aHR] 1.12; 95% CI, 0.92–1.36).

A 2004 prospective cohort (n=551) compared the effect of statin exposure versus no treatment in patients with systolic heart failure who were referred to a specialty clinic for clinical management or transplant evaluation.[2] Patients were recruited consecutively and included in the study if ejection fraction was measured at 40% or less. Average age of patients was 52 years old, although patients receiving statin therapy were significantly older (57 vs 48 years old, $P<.01$) and more likely to be male (82% vs 70%, $P<.01$). Ejection fraction on average was 25%, and 45% of patients had a diagnosis of CAD based on cardiac catheterization results. Statin exposure, without a specific dosage, was defined as already on therapy before referral and continued through study period or started within three months of the referral date and continued through the study period. Types of statins and dosing regimens were not specified. Patients with CAD were more likely to be on a statin during the study period compared with nonischemic patients (73% vs 22%). Over the one-year follow-up period, statin use was associated with significant improvement in survival without transplant for both CAD (hazard ratio [HR] 0.35; 95% CI, 0.19–0.62) and non-CAD patients (HR 0.27; 95% CI, 0.11–0.69) compared with the no statin treatment group. Death from any cause was significantly decreased in the statin group when controlling for NYHA class, presence of CAD, and other factors (aHR 0.41; 95% CI, 0.18–0.94). However, no difference was noted in rates of sudden cardiac death for the statin use group compared with the non-statin group (HR 0.47; 95% CI, 0.16–1.37). EBP

Jennifer MacDonald, MD
Christopher Benavente, MD
Mary Talen, PhD
Northwestern Family Medicine Residency Program
Chicago, IL

The authors declare no conflicts of interest.

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Do ICD's in patients with non-ischemic congestive heart failure with EF <35% improve mortality?

EVIDENCE-BASED ANSWER

Yes. In patients with congestive heart failure from nonischemic cardiomyopathy and a left ventricular ejection fraction of <35%, implantable cardioverter defibrillator (ICD) placement along with guideline-directed management and therapy improves all-cause mortality (SOR: **A**, based on meta-analysis of randomized controlled trial's and an evidence-based guideline). ICD placement is recommended for patients with an expected survival time of at least one year (SOR: **C**, expert opinion).

DOI 10.1097/EBP.0000000000001314

A 2017 meta-analysis of six randomized controlled trials (N=5,822) compared the benefit of ICDs vs medical management for all-cause mortality in patients with nonischemic cardiomyopathy.[1] Patients were a mean age of 60 years, majority male, with 50% hypertensive, and had a mean left ventricular ejection fraction

(LVEF) of 23%. Patients were randomized to receive an ICD (n=2,332) or medical therapy (n=3,490). An ICD is a battery-powered device placed under the skin with wires that connect it to the patient's heart to detect and abort abnormal heart rhythms by delivering an electric shock. These patients also received appropriate medical management. In the control group, some differences were noted in medical therapy. Although one trial used amiodarone alone, the remainder used a combination of beta-blockers, calcium channel blockers, nitrates, ace inhibitors, digoxin, diuretics, and anticoagulants. Medical therapy dosage and treatment duration was allowed to be managed by the prescribing physician. After pooling of all six trials, ICD implantation along with medical therapy significantly reduced all-cause mortality in nonischemic cardiomyopathy patients compared with those who received medical therapy alone (risk ratio [RR], 0.74; 95% CI, 0.56–0.97). In four of the trials, ICD implantation significantly reduced the risk of sudden cardiac death (RR, 0.47; 95% CI, 0.30–0.73) compared with medical therapy alone. Other secondary end points, such as risk of cardiac arrest, cardiac transplant, and ventricular tachycardia, showed no significant difference between the groups.

A 2017 evidence-based guideline from the American Heart Association/American College of Cardiology/Heart Rhythm Society covered ICD use in the management of ventricular arrhythmias and prevention of sudden cardiac death.[2] In patients with nonischemic cardiomyopathy heart failure with New York Heart Association class II to III symptoms and an LVEF of 35% or less, an ICD was recommended if meaningful survival of greater than one year is expected (Level of Evidence: **A**, recommended). EBP

Franklyn Babb, MD
Leon Chen, MD
Caom Hansen, MD
Khaled Attia, MD
Texas Tech Family Medicine Residency Program
Lubbock, TX

The authors declare no conflicts of interest.

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What is the relationship between lipoprotein(a) and CVD?

EVIDENCE-BASED ANSWER

Abnormally high lipoprotein (a) is strongly associated with an increased risk of mortality and morbidity secondary to adverse cardiovascular events, including but not limited to coronary artery disease (SOR: **A**, meta-analysis of randomized controlled trials and meta-analysis of cohorts).

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A 2018 meta-analysis of seven randomized controlled trials (N=29,069) examined the relationship between lipoprotein (a) levels and cardiovascular disease in patients on statin therapy.[1] Included patients had lipoprotein (a) readings at baseline and at the end of follow-up, were randomized to either statin therapy or placebo, and had a mean age of 62 years. Treatment duration and follow-up ranged from 16 weeks to over five years. Patients were stratified by baseline lipoprotein (a) levels of <15 mg/dL (n=8,574), 15 to 30 mg/dL (n=2,165), 30 to 50 mg/dL (n=1,546), and 50 mg/dL or greater (n=2,251). Oral once daily statin treatment (atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) was administered with standard dosing. The primary outcome was any general cardiovascular event, which included fatal or nonfatal coronary heart disease, stroke, or revascularization events. Results were adjusted for differences in previous disease status, diabetes, smoking, blood pressure, and cholesterol levels. After pooling of all seven trials, elevated lipoprotein (a) was associated with almost linear cardiovascular disease risk, especially for levels above 50 ml/

dL in both patients on statins and those on placebo. Patients with lipoprotein (a) levels of 50 mg/dL were significantly more likely to experience a general cardiovascular event compared with those in lower levels at both baseline (hazard ratio [HR], 1.3; 95% CI, 1.1–1.6) and at end of follow-up (HR, 1.4; 95% CI, 1.2–1.8). Limitations included differences in concentration calculations of lipoprotein (a) between studies, different time frames for follow-up measurements of lipoprotein (a), and the effect of any nonstatin lipid-modifying agents on cardiovascular risk could not be determined.

A 2017 systematic review of seven prospective cohorts (N=52,131) across Europe evaluated the association of regional differences in lipoprotein (a) levels and the relationship to adverse cardiovascular outcomes.[2] Participants were an average of 52 years old and had equal sex distribution. Maximum follow-up time was 24 years with a median follow-up of around nine years. Because of positive skewed distribution of lipoprotein (a) levels, 66th and 90th percentiles were 14.1 and 43.5 mg/dl, respectively. Participants in the 90th percentile of lipoprotein (a) levels had significantly higher rates of major coronary events (HR, 1.5; 95% CI, 1.3–1.7) and cardiovascular events (HR, 1.4; 95% CI, 1.3–1.7) compared with those in the lowest third percentile. EBP

Amit Sapra, MD, FAAFP
Shivani Sharma, MD
Asiya Mohammed, MD
Mohitkumar Ajmeri, MD
SIU Center for Family Medicine, Springfield, IL

The authors declare no conflicts of interest.

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Does daily supplementation with fish oil decrease atherosclerotic cardiovascular disease risk?

EVIDENCE-BASED ANSWER

For primary prevention, conflicting evidence exists on the value of using omega-3 supplementation to lower the risk of myocardial infarction, coronary heart disease (CHD) death, total CHD, cardiovascular (CVD) death, and total CVD (no recommendation given). Risk reductions may be related to omega-3 dose, with higher doses, up to 4,000 mg/day, showing some potential (SOR: **C**, mixed evidence from 2 large meta-analyses). Patients with known CHD may benefit from omega-3 supplementation for the secondary prevention of CVD events (SOR: **C**, evidence-based guidelines.)

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A 2019 meta-analysis of 13 randomized controlled trials (RCTs) (N=127,477) examined the effectiveness of marine omega-3 supplementation on the risk of cardiovascular (CVD).[1] Patients included were an average of 64 years old, 60% were male, 40% had diabetes mellitus, and 73% used cholesterol-lowering medication at the time of enrollment. Omega-3 supplementation doses ranged from 376 to 4,000 mg/d across studies. The majority of patients (73%) were supplemented on a dose between 840 and 1,000 mg/d and were treated for a mean duration of five years. Primary end points included myocardial infarction (MI), death from coronary heart disease (CHD), total stroke, death from CVD, total CHD, and major vascular events. Because one trial (n=8,179) was implementing an extremely high daily dose of 4,000 mg/d, separate analyses with and without the trial were conducted. In the

analysis excluding the high-dose trial (12 trials; N=119,298), patients in the supplementation group had a small but significant reduction in MI (rate ratio [RR], 0.92; 95% CI, 0.86–0.99), CHD death (RR, 0.92; 95% CI, 0.86–0.98), total CHD (RR, 0.95; 95% CI, 0.91–0.99), total stroke (RR, 1.05; 95% CI, 0.98–1.14), CVD death (RR, 0.93; 95% CI, 0.88–0.99), total CVD (RR, 0.97; 95% CI, 0.94–0.99), and major vascular events (RR, 0.97; 95% CI, 0.94–1.0) compared with placebo and control. Analysis including the high-dose trial demonstrated a significant dose-response relationship: per every 1,000 mg/d marine omega-3 supplementation, a 9% reduction in MI (95% CI, 2–15) and 7% reduction in total CHD (95% CI, 0.1–13) were noted. All other outcomes measured were not significantly different between the supplementation groups and the placebo/control groups.

A 2018 systematic review and meta-analysis of 79 RCTs (N=112,059) examined the effect of long-chain omega-3 fatty acid supplementation on CVD disease.[2] Patients in these studies had known CVD disease and were either treated as secondary (42%) or primary (58%) prevention, with pregnant and acutely ill patients excluded. Patients received varying long-chain omega-3 fatty acid doses with more than 90% of patients receiving 400 to 2,400 mg/d for between 12 and 72 months and were compared with placebo, different dietary advice, or no treatment. Compared with the control groups, patients who received omega-3 supplementation did not demonstrate a significant reduction in all-cause mortality (39 RCTs; N=92,653; RR, 0.98; 95% CI, 0.93–1.03), CVD mortality (25 RCTs; N=67,772; RR, 0.95; 95% CI, 0.87–1.03), or CVD events (38 RCTs; N=90,378; RR, 0.99; 95% CI, 0.94–1.04). Chronic heart disease mortality, stroke, and arrhythmia were also not significantly different between the groups. A significant 7% reduction in CHD events was initially noted; however, after adjustment for bias, no significant difference in the omega-3 group was found compared with the controls for overall CHD events (12 RCTs; N=30,227; RR, 0.97; 95% CI, 0.90–1.05).

A 2017 evidence-based science advisory from The American Heart Association (AHA) gave no recommendation on the use of omega-3 polyunsaturated fatty acid supplementation for the primary prevention of CHD.[3] The AHA did not recommend treatment with omega-3 poly unsaturated fatty acids for the primary prevention of CHD in patients with diabetes or for those with risk factors for CVD (strength: Class III, no proven benefit). However, they did recommend supplementation as secondary prevention in patients with known CHD (strength: Class IIa, weight of evidence/opinion is in favor of usefulness/efficacy). EBP

Eric Hellman, MD
Cecelia Murillo, MD
D. C. Ward, MD
Jamie Haynes, MD
Texas Tech Family Medicine Residency
Lubbock, TX

The authors declare no conflict of interest.

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In patients with cirrhosis, which beta-blockers are most effective for decreasing risk of bleeding from esophageal varices?

EVIDENCE-BASED ANSWER

Carvedilol is more effective than nonselective beta-blockers (NSBBs) at reducing hepatic venous gradient pressure (SOR: **C**, disease-oriented evidence from meta-analysis of RCTs) but has no clear increased benefit for bleeding, mortality, or serious or nonserious adverse events (SOR: **A**, meta-analysis of RCTs and single RCT). Carvedilol is comparable with propranolol in safety and efficacy in regard to cirrhosis decompensation (SOR: **B**, single RCT).

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A 2018 systematic review and meta-analysis of 11 RCTs (N=810) examined the efficacy of carvedilol

versus traditional NSBBs for primary and secondary prevention of gastroesophageal varices in adults with cirrhosis in an outpatient setting.[1] Patients were adults with cirrhosis and endoscopically or radiologically verified gastroesophageal varices. Most had cirrhosis secondary to alcohol overuse (59%) or chronic hepatitis (27%). Beta-blocker dosing varied between trials, with carvedilol groups receiving a mean dose of 13 mg per day (range 6–31 mg). Control groups received NSBB therapy with either propranolol (9 trials), mean dose 74 mg (range 18–150 mg) per day, or nadolol (1 trial), mean dose 45 mg (range 20–80 mg) per day. Treatment duration was less than three months in six trials and greater than three months in five trials. The primary outcomes were all-cause mortality, upper gastrointestinal bleeding, and serious adverse events defined as life-threatening events that required hospitalization or prolonged an existing hospitalization. Secondary outcomes included nonserious adverse events and treatment failure defined as failure to achieve a reduction in hepatic venous pressure gradient (HVPG, a marker of variceal bleeding risk) by 12 mmHg or by at least 20%. When compared with the NSBB group, no significant difference was noted in the carvedilol group for mortality rate (7 trials; N=507; relative risk [RR] 0.86; 95% CI, 0.48–1.5), upper gastrointestinal bleeding (10 trials; n=810; RR 0.77; 95% CI, 0.43–1.4), or serious adverse events (10 trials; N=810; RR 0.97; 95% CI, 0.67–1.4). Carvedilol was associated with a significant reduction in HVPG at the end of treatment (mean difference [MD] –1.8 mmHg; 95% CI, –2.6 to –0.89 mmHg) and in HVPG percentage change from baseline (MD –8.0%; 95% CI, –12% to –4.7%) compared with the NSBB group. No differences between carvedilol and NSBBs were observed in nonserious adverse events. Limitations of this study included underpowered sample sizes among studies and variations in beta-blocker dosing.

A 2019 multicenter double-blinded RCT (n=201) compared the effectiveness of beta-blocker therapy (propranolol and carvedilol) versus placebo in prevention of decompensation of cirrhosis.[2] Patients (mean of 60 years old) were adults from a single hospital setting in Spain with compensated cirrhosis (80% of participants had Child-Pugh class A) having clinically significant portal hypertension. Patients needed to have a portal pressure gradient of 10 mmHg or greater to meet the criteria for clinically significant portal hypertension. Patients were excluded if they had previous cirrhosis decompensation, portal thrombosis, or previous treatment with β-blockers or nitrates. Participants were stratified to intervention groups based on HVPG response during the 3-week open-label titration period. HVPG responders (with a decrease in 10% or greater in HVPG from baseline) were randomized to treatment with 40 to 160 mg propranolol twice daily (n=67) or placebo (n=68). Patients with a decrease in HVPG less than 10% on propranolol were randomized to treatment with 6.3 to 25 mg carvedilol daily (n=33) or placebo (n=33). Medications were titrated to achieve a heart rate greater than 55 beats per minute and a systolic blood pressure of 90 mmHg or greater. Patients were then tracked until the incidence of cirrhosis decompensation; defined as ascites, bleeding, or overt encephalopathy or death. If decomposition did occur, treatment was discontinued. Secondary outcomes included development of complications of portal hypertension, spontaneous bacterial peritonitis and other bacterial infections, variceal bleeding, changes in hepatic dysfunction, hepatocellular carcinoma, and adverse events. The combined outcome of decomposition or death was significantly lower in the beta-blocker versus placebo group (hazard ratio [HR] 0.49; 95% CI, 0.24–0.98); however, no difference in rates of decompensation or death was noted between propranolol (HR 0.69; 95% CI, 0.34–1.4) and carvedilol (HR 0.39; 95% CI, 0.10–1.5). Beta-blockers were beneficial in preventing decompensation in patients with small varices (HR 0.45; 95% CI, 0.20–0.98) and in those with nonalcoholic cirrhosis (HR 0.20; 95% CI, 0.26–0.97). Carvedilol significantly decreased HVPG versus propranolol at both 12 months (16% vs 10%, $P=.04$) and 24 months (15% vs 9%, $P=.05$). No differences were reported in beta-blocker group versus placebo in hepatic encephalopathy spontaneous bacterial peritonitis and other bacterial infections. EBP

Samantha DeMarco, PharmD, BCPS
Sehrish Panjwani, PharmD, BCPS
Marianne Koenig, PharmD, BCPS
UPMC St. Margaret
Pittsburgh, PA

The authors declare no conflicts of interest.

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In adults with obesity-related comorbidities which behavior change techniques decrease weight?

EVIDENCE-BASED ANSWER

Cognitive behavioral therapy interventions are effective in promoting a small to moderate change in weight loss (SOR: **A,** meta-analysis of randomized controlled trials [RCTs]). Mindfulness interventions do not demonstrate significant changes in weight loss (SOR: **A,** meta-analysis of RCTs). Web- and computer-based behavioral interventions promote moderate weight loss compared with control but are less effective than in-person interventions (SOR: **A,** meta-analysis of RCTs).

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A 2018 meta-analysis of 12 randomized controlled trials (RCTs; N=6,805) compared cognitive behavioral therapy (CBT) weight loss interventions with behavioral only techniques or usual care in overweight and obese adults.[1] Patients were majority female with a mean age of 45 years and had an average body mass index (BMI) between 29 and 38 kg/m^2. Patients with underlying chronic diseases with potential weight effects, such as cancer or coronary artery disease, were excluded, although those with asthma and/or diabetes were included. CBT techniques included problem solving (4 trials), pattern recognition (3 trials), acceptance-based strategies (3 trials), relapse prevention (3 trials), and cognitive restructuring (2 trials). Comparison techniques included usual care, education, and/or non-CBT behavioral techniques (eg, stimulus control, self-monitoring, goal setting). Overall, patients averaged 27 sessions over a period of 1 to 48 months. Follow-up ranged from 4 to 162 months, with most studies around 12 months of total follow-up. Because of high variance among scoring scales used, results were pooled and converted to effect sizes (ES). After pooling of all 12 trials, patients in the CBT group experienced a small, significant improvement in overall weight loss compared with the usual care and nonbehavioral groups (pooled ES, 0.30; 95% CI, 0.09–0.51). It should be noted that 75% of patients in the pooled analysis came from a single trial of patients with type-2 diabetes and with the longest treatment period.

A 2017 meta-analysis of 12 RCTs (N=626) evaluated the effects of mindfulness training on weight loss and health behaviors.[2] Patients all had a BMI above 25.0 kg/m^2, with almost all trials averaging a BMI in the obese or greater range. Patients were majority female with a mean age around 46 years, although one trial targeted college students with an average age of 20 years. Mindfulness training interventions included Mindfulness-Based Stress Reduction (2 trials), Mindfulness-Based Eating Awareness Training (3 trials), Adapted Mindfulness Interventions (2 trials), Acceptance and Commitment Therapy (ACT) (2 trials), and a yoga/meditation program (1 trial). Sessions were held approximately weekly and ran for 8 to 24 weeks, except for ACT programs, which were a single 6-hour session. Comparison groups included treatment as usual, waitlist, and information only programs. BMI was assessed 8 to 24 weeks post program initiation. The pooled analysis demonstrated no significant difference in BMI between the mindfulness groups and the control groups (9 trials; N=597; mean difference [MD], –0.15 kg/m^2; 95% CI, –0.59 to 0.29 kg/m^2).

A 2012 meta-analysis of 14 RCTs (N=2,537) evaluated the efficacy of delivering behavioral change therapy using technology rather than traditional in-person behavioral therapy.[3] Patients were majority female (82%), with a mean age of 42 years, and a mean BMI of 32 kg/m^2. Multiple behavioral change techniques were used, including goal setting, problem solving, and reinforcement tactics. Web- and computer-based interventions included goal setting tools, alarm reminders, food and exercise trackers, and social networking tools versus in-person behavioral therapy or minimal and informational only web-based intervention. Patients attended a single introductory session and then were asked to engage with

the program daily. Those enrolled in in-person behavioral therapy sessions met weekly. Interventions lasted between four weeks and 30 months, with weight recorded six months post intervention. Patients in the web-based behavioral change therapy groups lost significantly more weight compared with the information-only group (2 trials; n=511; MD, –1.5 kg; 95% CI, –2.1 to –0.9 kg) at six months. However, when compared with in-person interventions, participants in the technology-based modality lost less weight (MD, 2.1 kg; 95% CI, 0.8–3.4). Additionally, one trial (n=62) reported a cost-effectiveness ratio for an in-person weight loss intervention relative to a computer-based intervention as $7,177 per life of year gained. High levels of heterogeneity were observed between studies and in participant technology usage. Additionally, given multiple changes in technology since this study was published, the outcomes may have lost relevance and applicability. EBP

Laura Padhye, MD
Christine Danner, PhD, LP
Kathryn Freeman, MD
University of Minnesota Department of Family Medicine and Community Health, Saint Paul, MN

The authors declare no conflicts of interest.

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Does fish oil supplementation improve cognition in adults?

EVIDENCE-BASED ANSWER

Omega-3 polyunsaturated fatty acids supplementation in adults with mild cognitive impairment or age-related cognitive decline may mildly improve immediate recall (effect size [ES] 0.16) and attention and processing speed (ES 0.30) (SOR: **B**, 1 meta-analysis). Fish oil supplementation does not improve cognition in adults with Alzheimer dementia or normal cognition (SOR: **A**, meta-analyses and subsequent randomized controlled trial).

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A 2012 meta-analysis of 10 double-blinded, randomized controlled trials (RCTs; N=2,507) studied the effects of omega-3 polyunsaturated fatty acids (n-3 PUFA) supplementation on cognitive performance.[1] Patients were 50 years old or older and were classified as cognitively healthy elderly adults, elderly adults with memory complaints and objective cognitive decline, or elderly adults with known dementia or Alzheimer disease. Primary outcomes evaluated across the various trials included composite memory, immediate and delayed recall, recognition and working memory, attention and processing speed, and global cognitive function. Patients were evaluated with multiple validated cognitive function tests including the Mini-Mental State Examination (MMSE; scoring range 0–30, with lower numbers indicating cognitive loss) and the Alzheimer's Disease Assessment Scale (ADAS-Cog). ADAS-Cog is a 70-point questionnaire, with higher scores (≥18) correlating to greater cognitive impairment. Participants were excluded if they had a psychiatric comorbidity. The intervention group was supplemented with n-3 PUFAs consisting of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (240–1,940 mg/d) between 15 and 108 weeks. N-3 PUFA supplementation mildly improved immediate recall (4 trials; N=676; ES 0.16; 95% CI, 0.01–0.31) and attention and processing speed (3 trials; N=193; ES 0.30; 95% CI, 0.02–0.57) in individuals in the mild cognitive impairment or age-related cognitive impairment group. Supplementation provided no cognitive benefit to patients with established Alzheimer disease or the cognitively healthy. Limitations included variation across studies of patient groups, assessment procedures, and treatment formulations.

A 2012 meta-analysis of three RCTs (N=4,080) evaluated the effects of n-3 PUFA supplementation for the prevention of cognitive decline and dementia in older adults.[2]

Two of the three studies were included in the above meta-analysis. Patients were 60 years old or older and deemed cognitively healthy at enrollment with MMSE scores >21 or 24. Patients who did not meet MMSE score minimum, had known dementia, were being treated for dementia or depression, or already taking n-3 supplementation were excluded. Participants received supplementation of fish oil with 700 mg/d EPA-DHA over 24 months, 400 mg/d EPA-DHA over 40 months, and 1,940 mg/d or 400 mg/d EPA-DHA over six months compared with placebo of either sunflower or olive oil. Cognitive health was measured by validated cognitive function tests including MMSE, Word Learning Test (immediate and delayed recall), Verbal Fluency Test, and Wechsler Digit span tests (forward and backward) performed between 24 and 48 months. No statistical difference between intervention and control groups in MMSE scores (2 trials; N=3,221; mean difference [MD] –0.7; 95% CI, –0.25 to 0.10), immediate recall (3 trials; N=1,043; standardized mean difference [SMD] 0.01; 95% CI, –0.11 to 0.14), delayed recall (3 trials; N=1,043; SMD −0.04; 95% CI, –0.16 to 0.09), word recognition (3 trials; N=1,042; SMD 0.04; 95% CI, –0.08 to 0.16), verbal fluency test (3 trials; N=1,042; SMD 0.06; 95% CI, –0.06 to 0.18), digit span forward (3 trials; N=1,018; MD 0.03; 95% CI, –0.25 to 0.31), and digit span backward (3 trials; N=1,015; MD 0.12; 95% CI, –0.12 to 0.36).

A 2018 RCT (n=403) compared cognitive performance between adults supplemented with n-3 PUFA and placebo (olive oil) in Australia.[3] The trial included cognitively healthy 65- to 90-year-olds (MMSE>22) who were supplemented daily with 2.3 g of fish oil (600 mg EPA+1720 mg DHA) or placebo for 18 months. Participants were excluded if they had prior n-3 supplementation, English language difficulty, or had current or past medical history of cognitive impairment (stroke, head injury, diabetes, alcohol, or drug abuse). They were followed at 6-month intervals for serial cognitive testing via latent growth curve models on reasoning, working memory, short-term memory, retrieval fluency, and cognitive speed. Supplementation resulted in no improvement in cognitive performance for reasoning (ES 0.15; 95% CI, –0.03 to 0.23), short-term memory (ES 0.02; 95% CI, –0.08 to 0.12), working memory (ES 0.01; 95% CI, –0.29 to 0.37), or retrieval fluency (ES 0.09; 95% CI, –0.22 to 0.04). Supplementation did result in a small negative effect on psychomotor speed (ES –0.02; 95% CI, –0.04 to 0.00). The study was limited by the population evaluated because they had higher levels of education to begin with, possibly too short of a follow-up period, and is at risk of type I error. EBP

Stephen Cagle, MD
Vincent Duenas, MD
Southwestern Illinois Family Medicine Residency
O'Fallon, IL

The authors declare no conflict of interest.

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Does OMT improve pelvic pain in pregnancy?

EVIDENCE-BASED ANSWER

Yes. Osteopathic manipulative treatment is effective in decreasing pregnancy-related pelvic pain and increasing overall functional status (SOR: **A**, 2 large systematic reviews of randomized controlled trials [RCTs]) but is no more effective than sham procedures (SOR: **B**, systematic review of RCTs).

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A 2017 systematic review of eight randomized controlled trials (RCTs; N=857) examined the effectiveness of osteopathic manipulative treatment (OMT) on both low back pain and pelvic pain in pregnant women.[1] A subanalysis of five RCTs (N=677) that specifically examined OMT during pregnancy was identified. Three of the five trials in this subanalysis were not published. Patients were at least 18 years old, from the United States and Germany, and had nonspecific low back pain or pelvic pain. Women with

specific reasons for low back pain or pelvic pain such as tumor, infection, or fracture were excluded from the review. Treatments were completed by osteopaths and osteopathic physicians per the examiners' clinical judgment and not standardized to the same protocol. Specific techniques used included soft tissue, joint mobilization, stretching, muscle energy, spinal manipulation, visceral, and cranial. The control groups received usual obstetric care with no OMT. The duration of treatment ranged from 4 to 9 weeks. Because of heterogeneity in pain and function measures, results were pooled and standardized to a 1 to 100 pain scale with higher scores indicating worsening pain and to a standardized mean difference (SMD) for functional measures. After pooling of the five trials, OMT had a medium-sized effect on decreasing pain (mean difference [MD], –17; 95% CI, –32 to –1.7) and increasing functional status (SMD, –0.5; 95% CI, –0.93 to –0.07) compared with the control group.

A 2016 systematic review and meta-analysis of 10 RCTs (N=1,198) analyzed the effectiveness of manual therapies on reducing pregnancy-related back and pelvic pain.[2] Patients were pregnant women (median age, 29 years) from United States, Poland, Germany, and Sweden with primary outcomes of low back pain and pelvic girdle pain intensity. No exclusion criteria were provided. Manual therapies included cranial sacral therapy, osteopathic manipulative treatment, chiropractic, massage, and partner-delivered massage. Subgroup analysis by type of manual therapy intervention was not conducted because of the limited number of trials. Patients received between four and 32 sessions over 2 to 16 weeks (once per month to 5 times a week), each session lasting 15 to 45 minutes. Once again results were pooled and converted into a SMD. Overall, a large improvement was noted in low back pain and pelvic pain in pregnancy with manual therapies when compared usual care (8 trials; n=1,115; SMD, –0.70; 95% CI, –1.1 to –0.30) and compared with relaxation (2 trials; n=110; SMD, –0.77; 95% CI, –1.2 to –0.32), but no improvement was noted when compared with sham procedures (2 trials; n=544; SMD, 0.05; 95% CI, –0.15 to 0.26). EBP

Alex Harmony, DO
Julia Hamilton, DO
St. Peter Family Medicine Residency, Olympia, WA

The authors declare no conflicts of interest.

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Does rifaximin decrease small intestinal bacterial overgrowth in patients with irritable bowel syndrome?

EVIDENCE-BASED ANSWER

Rifaximin is effective in reducing small intestinal bacterial overgrowth in patients with irritable bowel syndrome via the normalization of lactulose hydrogen breath test scores (SOR: **C**, disease-oriented evidence from a meta-analysis of cohorts and secondary analysis from randomized controlled trial [RCT]). However, this normalization is likely because of secondary changes in the small intestinal flora immediately after treatment and improvements are often short-lived (SOR: **C**, consistent disease-oriented evidence from secondary analysis of RCT and observational trial).

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A 2017 systematic review and meta-analysis of seven RCTs and 24 cohort studies evaluated the efficacy of rifaximin to eradicate SIBO.[1] Patients had a confirmed diagnosis of SIBO, were 18 years old or older, and did not have neoplastic disease. A subanalysis of cohorts specifically examining SIBO in patients with irritable bowel syndrome (IBS) for both intention-to-treat analysis (6 cohorts; N=311) and per-protocol analysis (10 cohorts; N=427) was identified. Glucose hydrogen breath tests and lactulose hydrogen breath test (LHBT) were used to diagnose

and assess eradication of SIBO. Oral rifaximin doses ranged from 800 to 1,200 mg orally daily for 7 to 28 days, with most studies using 1,200 mg orally daily for 7 to 14 days. Follow-up time ranged from end of treatment to five months. The pooled eradication rate indicated moderate treatment success in both the intention-to-treat group (rate 72%; 95% CI, 57%–84%; I^2=86%) and the per-protocol group (rate 75%; 95% CI, 65%–85%; I^2=82%).

A 2019 secondary analysis (n=103) of an RCT evaluated the microbiologic effects of rifaximin on SIBO in patients with diarrhea predominant IBS.[2] Majority of the patients were White females with a median age of 48 years old. Rome III criteria were used for diagnosis of IBS, and patients were excluded if taking probiotics or any antibiotic within 14 days of randomization. All patients received open-label rifaximin 550 mg orally three times daily for two weeks, then the clinical response rate was evaluated four weeks posttreatment. Patients with symptom relapse were further randomized to receive two additional courses of rifaximin (n=37) or placebo (n=36), each separated by 10 weeks and then evaluated for changes in fecal microbiologic makeup. Fecal samples were collected before and after both the open-label rifaximin treatment and first subsequent rifaximin course, and at study completion (8 weeks after final treatment). Results were based on 675 fecal samples that generated 2,309,172,633 paired bacterial 16S ribosomal RNA sequence reads. Overall population decreases in seven bacterial families, including Enterobacteriaceae, Verrucomicrobiaceae, Peptostreptococcaceae, Pasteurellaceae, Synergistaceae, Eubacteriaceae, and Enterococcaceae, between the pre-open and post-open rifaximin course were found. However, the authors stated that when comparing bacterial ribosomal RNA from baseline to final time point, no significant difference in the small intestinal bacterial populations was seen between individuals treated with rifaximin and placebo (no numbers or statistics provided).

A 2015 8-week open-labeled observational trial (n=15) evaluated the effect of rifaximin on gut microbiota in patients with nonconstipation IBS.[3] IBS diagnosis was determined by Rome II criteria, and any patient with diabetes, gastrointestinal disease or surgery history, or cardiac disease were excluded. Patients received rifaximin 550 mg orally three times daily for 14 days. LHBTs and fecal sample collections were performed at baseline, day 14, and at eight weeks. At baseline, 12 patients had a diagnosis of SIBO via LHBT. A negative LHBT was reported in 11 patients (92%) at day 14, 10 patients (83%) at eight weeks, and nine patients (75%) at both day 14 and eight weeks. Authors concluded that although an improvement in LHBT was noted, no statistical change was noted in the overall composition of microbiota in stool samples by week eight. For example, Clostridiaceae composed 0.89% of the combined stool samples at baseline, 0.1% at day 14, and 1.6% at week eight. EBP

Kent Wright, MD
Paul Middleton, MD
Jonell Hudson, PharmD, BCPS
Lois Coulter, PharmD, BCPS
Brittany Vaughn, MD
UAMS Northwest FMR, Fayetteville, AR

The authors declare no conflicts of interest.

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What is the best treatment of methamphetamine use disorder?

EVIDENCE-BASED ANSWER

A combination of contingency management and community reinforcement is the most effective and acceptable intervention for both short- and long-term treatment of individuals with amphetamine addiction. This combination increases the odds of abstinence at 12 weeks of treatment and at the longest follow-up after treatment (2 years) by 2 to 4 times compared with other psychosocial interventions (SOR: **A**, meta-analysis of good-quality randomized controlled trials [RCTs]). No pharmacotherapy evaluated for methamphetamine use disorder treatment has had strong or consistent evidence of benefit in abstinence or treatment retention (SOR: **A**, meta-analysis of good-quality RCTs).

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A 2018 systematic review and network meta-analysis of 50 RCTs (N=6,942) evaluated psychosocial interventions or treatment as usual for cocaine and amphetamine addiction in adults.[1] Mean participant age was 36.8 years old, and 35.9% were women. Twenty-two of the 50 trials enrolled patients with amphetamine or amphetamine plus cocaine addiction and had durations between six and 48 weeks. Outcomes measured were as follows: 1) proportion of patients with urinalysis confirmed abstinence at 12 weeks and at the end of treatment; 2) longest duration of abstinence; and 3) proportion of patients who dropped out because of any cause by the end of treatment. Twelve different psychosocial interventions (see **TABLE**; including combinations of treatments) and treatment as usual were compared with each other. Contingency management combined with a community reinforcement approach improved abstinence at 12 weeks in comparison with four of the other interventions (odds ratio [OR] range, 2.43–4.07). The contingency management plus community reinforcement approach also had fewer dropouts in comparison with all but two of the other interventions (OR range, 2.25–4.61). This combination also increased patient abstinence at the end of treatment (OR 2.84; 95% CI, 1.24–6.51; P=.013) and at longest follow-up at 96 weeks (OR 3.08; 95% CI, 1.33–7.17; P=.008) compared with treatment as usual. Many studies were small and not well blinded.

A 2019 systematic review and meta-analysis of RCTs (N=3,060) examined the effectiveness of pharmacotherapy for methamphetamine and amphetamine use disorder.[2] It included one systematic review and 17 RCTs, with sample sizes ranging from 19 to 299 patients and a mean enrollment of 90. Trials enrolled nonpregnant adults and excluded patients with psychotic spectrum and bipolar disorder. Seventeen different medications were evaluated, including antidepressants, antipsychotics, psychostimulants, anticonvulsants, and opioid antagonists. Outcomes

TABLE. Psychosocial interventions investigated for methamphetamine use disorder[1]

Intervention	Brief Description
12-step program	A mutual aid organization for the purpose of recovery from substance addictions, behavioral addictions, and compulsions
Contingency management	Rewards for verified drug-free urine samples
Community reinforcement approach	Multilayered interventions including functional analysis, coping-skills training, and social, familial, recreational, and vocational reinforcements
Cognitive behavioral therapy	Evidence-based, form of psychological therapy
Meditation-based treatment	Trained guidance in breathing and meditations
Noncontingent rewards	Delivering rewards independent of the occurrence of any specified behavior
supportive-expressive psychodynamic therapy	Psychological interpretation of mental and emotional processes; rooted in traditional psychoanalysis

measured were as follows: 1) urine drug screening confirmed abstinence for three or more consecutive weeks; 2) the proportion of negative urine drug screen specimens; and 3) treatment retention. None of the drug classes evaluated for methamphetamine use disorder treatment had strong or consistent evidence of benefit in abstinence or treatment retention. Antidepressants as a class had no effect on abstinence or retention. Anticonvulsants, antipsychotics, opioid antagonists, topiramate, varenicline, and atomoxetine did not improve any of the outcomes. Low strength evidence suggested that methylphenidate may reduce methamphetamine use (OR 0.46; 95% CI, 0.26–0.81; $P=.008$); however, no effect was noted on treatment retention. The main limitations of this study were its broad scope, its restriction to English-only literature, and its reliance on previously published systematic reviews. EBP

Micheal C. Irelan, MD
Armando Quiroz, MD
Robert Marshall, MD, MPH, MISM, FAAFP, FAMIA
Madigan Army Medical Center
Joint Base Lewis-McChord, WA

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Does surgery improve outcomes in chronic lateral epicondylitis?

EVIDENCE-BASED ANSWER

Maybe. Surgery seems to improve pain and function, but improvements are small, of questionable clinical relevance, and have not been shown to be superior to other therapies such as shockwave therapy (SOR: **B**, systematic review of small randomized controlled trials [RCTs]). There is no difference between open or arthroscopic debridement in pain or function postoperatively (SOR: **B**, meta-analysis of RCTs, cohorts, and a case-control study).

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A 2011 systematic review of five randomized controlled trials (RCTs; N=191) compared various surgical interventions for the treatment of chronic lateral epicondylitis.[1] Patients were both men and women, 22 to 72 years old, with at least five months of chronic lateral elbow pain who failed conservative treatment (physiotherapy, steroid injections, or NSAIDs) and had no history of trauma or systemic inflammatory conditions. One trial (n=47) compared open release of extensor carpi radialis brevis (ECRB) tendon to percutaneous tenotomy for improvement in Disability of the Arm, Shoulder, Hand (DASH) score (range 0–100) and time to return to work. After 12 months, there was no difference in DASH scores between open release of ECRB tendon and percutaneous tenotomy (mean difference [MD] –3.0; 95% CI, –6.6 to 0.6). Patients who had percutaneous tenotomy did return to work sooner than those who had open release of ECRB tendon (MD –3.0 weeks; 95% CI, –3.6 to –2.3 weeks). A second trial (n=24) compared open release of ECRB tendon to radiofrequency microtenotomy for improvements in pain (range 0–10), elbow function (range 0–100), and grip strength (kilograms) over 12 weeks postprocedure. There was no significant difference in pain scores, elbow function, or in grip strength compared with baseline between the two groups at any time over the 12 weeks. A third trial (n=56) compared shock wave therapy (1 session of 1,500 shocks delivered to area of maximal tenderness) with percutaneous tenotomy for improvements in pain at night, pain at rest, and pain with pressure. Patients were followed for 52 weeks and measured differences in pain with a 0–100 visual

analog scale (VAS). At 52 weeks, there was no significant improvement for those in surgical group compared with the shock group in pain at rest (MD –2.0; 95% CI, –5.9 to 1.9) or pain with pressure (MD 0; 95% CI, –7.0 to 6.9). A slight significant improvement was found in pain at night in those receiving shock wave therapy compared with tenotomy (MD 5.0; 95% CI, 1.1–8.9). However, this improvement was small and of little clinical significance. Both remaining trials comparing open ECRB surgery with either botulinum injections or nerve decompression also found no differences between groups in pain improvement. The authors concluded there was insufficient evidence about the benefits of surgical interventions and the included trials were highly susceptible to bias.

A 2019 systematic review and meta-analysis of three retrospective cohorts, two RCTs, and one case-control study (N=608) compared arthroscopic debridement (n=376) and open debridement (n=232) of ECRB in the management of lateral epicondylitis.[2] Arthroscopic debridement of the ECRB tendon is a less invasive alternative to open debridement. Patients had an average age of 45 to 54 years old and all reported lateral elbow pain for at least six months before procedure. Open and arthroscopic debridement groups were compared for differences in failure rate, as defined by a poor outcome or the need for additional surgical intervention. Both groups were also compared for differences in function, which was measured by VAS or a DASH score, and complication rates. Total follow-up ranged from 12 to 94 months. There was no difference in failure rate between patients in the open and arthroscopic procedures (4 studies; N=479; risk ratio [RR] 0.89; 95% CI, 0.38–2.1). There was also no difference in DASH score (3 studies; N=438; MD –1.3; CI, –3.2 to 0.60) or VAS score (4 studies; N=238) between groups. Because of variable pain scales used and limited reported mean and standard deviations, no pooling was conducted for VAS scores. However, all studies reported that there was no significant difference between VAS scores in the arthroscopic and open groups. Complication rates were similar between the arthroscopic and open groups (4 studies; N=468; 1.0% vs 0.6%, $P>.05$). EBP

Avery Tucker, DO
Kristin Eide, DO
Smiley's Family Medicine Program
University of Minnesota
Minneapolis, MN

The authors declare no conflict of interest.

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Does supervised moderate-intensity aerobic exercise relieve pain symptoms in patients with fibromyalgia?

EVIDENCE-BASED ANSWER

Yes, but the response may not be clinically significant. Land-based aerobic exercise reduces pain by up to 11% in patients with fibromyalgia, whereas aquatic aerobic exercise reduces pain by up to 7% (SOR: **B**, meta-analysis of randomized controlled trials rated as low quality). Aerobic and resistance exercises are recommended in patients with fibromyalgia to relieve pain and improve physical function (SOR: **C**, expert opinion).

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A 2017 meta-analysis of six randomized controlled trials (RCTs; N=351) examined the effectiveness of land-based aerobic exercise training for the treatment of adult fibromyalgia pain.[1] The patients (mean ages 33–55

years, 99% female) were diagnosed with fibromyalgia based on American College of Rheumatology 1990 or 2010 criteria. Severity of fibromyalgia was not described. The intervention groups were enrolled in supervised activities such as walking, stationary bike, and rhythmical movements 2 to 5 times per week for a duration of 6 to 24 weeks. Intensity of exercise ranged from light to vigorous based on percent of maximum heart rate. The control groups were patients who did not receive an exercise program or received no change in current management of fibromyalgia. Pain intensity was reported in visual analogue scale (VAS, range 0–100), with follow-up ranging from immediately poststudy to four years. Land-based aerobic exercise improved pain scores compared with control groups (mean difference [MD] –11.1; 95% CI, –18.3 to –3.8; number needed to treat [NNT]=4), but this result may not be clinically meaningful as the commonly considered minimum difference for clinical significance is 15. Limitations included trial heterogeneity for type, duration, and frequency of aerobic exercise, and variation in controls. The meta-analysis authors considered the evidence low quality because the trials had a high risk of detection, performance, attrition, and reporting bias.

A 2014 meta-analysis of seven RCTs (N=382) examined the effect of aquatic aerobic exercise training on the treatment of adult fibromyalgia pain.[2] The trials included solely female participants with a mean age of 43 to 51 years old. The intervention group participated in supervised group aquatic activities ranging from 1 to 3 times per week for a duration of 10 to 34 weeks. Exercise intensity ranged from light to vigorous based on percent of maximum heart rate or as tolerated based on pain and fatigue. Control groups varied widely from no change in physical activity to other interventions. Pain was assessed using VAS before and after the intervention. Aquatic aerobic exercise improved pain scores compared with the control group (MD –6.6; 95% CI, –10.71 to –2.5; NNT=5). Limitations included small sample size with heterogenous exercise and control interventions, as well as high risk of detection and reporting bias.

The 2017 European League Against Rheumatism Revised Recommendations for the Management of Fibromyalgia makes a "strong" recommendation for aerobic and resistance exercise as a component of fibromyalgia treatment.[3] This recommendation was based on expert consensus and systematic reviews demonstrating improvement in pain and physical function. EBP

Andrew Smith, MD
Alan Gill, MD
Tacoma Family Medicine, Tacoma, WA

The authors declare no conflicts of interest.

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Does routine iron supplementation improve anemia or health outcomes in menstruating women?

EVIDENCE-BASED ANSWER

Routine daily iron supplementation reduces anemia incidence by 61% (number needed to treat [NNT]=3) but comes with an increased risk of gastrointestinal (GI) side effects (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Intermittent iron supplementation is associated with a 35% reduction in incidence of anemia (NNT=8) without increased risk of GI side effects (SOR: **A**, meta-analysis of RCTs).

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A 2016 meta-analysis of 67 randomized controlled trials (RCTs; N=8,506) examined the effect of daily iron supplementation on anemia and iron status in menstruating women.[1] All patients were women, 12 to 50 years old, across multiple continents. Acutely or chronically ill patients and those with abnormal iron metabolism or erythropoiesis were excluded. The women were given iron supplementation (with or without folic acid or vitamin C) at least five days per week for 1 to 24 weeks with similar follow-up time

frames. Dosing was 1 to 300 mg of elemental iron as ferrous sulfate, ferrous gluconate, ferrous fumarate, carbonyl or colloidal iron in tablet, capsule, and liquid form. Control groups received placebo or nothing. Prespecified primary outcomes were anemia (using study-specific hemoglobin cutoffs), mean difference (MD) hemoglobin (Hb) concentration, iron deficiency (using indices such as ferritin), all-cause mortality, and adverse effects. When compared with placebo, iron supplementation decreased the incidence of anemia (10 RCTs; N=3,273; RR 0.39; 95% CI, 0.25–0.60; number needed to treat [NNT]=3), increased the Hb concentration (51 RCTs; N=6,861; MD 5.3 g/L; 95% CI, 4.1–6.5), and decreased the rate of iron deficiency (7 RCTs; N=1,088; RR 0.62; 95% CI, 0.50–0.76). Insufficient evidence exists to evaluate the effect of iron supplementation on all-cause mortality. When compared with placebo, iron supplementation increased the risk of gastrointestinal side effects (5 RCTs; N=521; RR 2.0; 95% CI, 1.3–3.1), loose stools/diarrhea (6 RCTs; N=604; RR 2.1; 95% CI, 1.1–4.1), and constipation (8 RCTs; N=1,036; RR 2.1; 95% CI, 1.4–3.2). Limitations included a high risk of bias because of inadequate reporting of blinding, randomization, and allocation concealment; differential attrition across groups; and inconsistent outcomes reporting.

A 2019 meta-analysis of 25 RCTs (N=10,996) examined the effect of intermittent iron supplementation on anemia compared with placebo or no treatment.[2] The trials included postmenarchal, premenopausal, nonpregnant and nonlactating women from low- to middle-income countries and one Western European country. Severely anemic patients (Hb<8 g/dL) and those with conditions preventing menstruation were excluded. Included trials evaluated once, twice, or thrice weekly intermittent iron for 3 to 12 months at doses of 10 to 120 mg elemental ferrous sulfate, ferrous fumarate, or ferrous chloride, with or without folic acid or vitamin C. Comparison groups received either placebo or no intervention. Prespecified primary outcomes were anemia (Hb concentration below trial-defined threshold), MD Hb concentration, iron deficiency, ferritin, and all-cause mortality. Follow-up periods were variable and up to one year. When compared with placebo or no treatment, intermittent iron supplementation decreased the incidence of anemia (11 RCTs; N=3,135; RR 0.65; 95% CI, 0.49–0.87, NNT=8), increased Hb concentration (15 RCTs; N=2,886; MD 5.2 g/L; 95% CI, 3.1–7.3), and increased ferritin (7 RCTs; N=1,067; MD 7.5 μg/L; 95% CI, 5.0–9.9). Insufficient evidence exists to evaluate intermittent iron supplementation's effect on iron deficiency and all-cause mortality. No statistically significant differences were noted between the intervention and control groups with regard to diarrhea and adverse effects. Limitations included high risk of bias because of lack of adequate reporting on randomization and allocation concealment, selective reporting bias, incomplete outcome data reporting, and lack of blinding. EBP

Joshua Marshak, MD
Katherine Landy, MD, MPH
Tacoma Family Medicine Residency Program
Tacoma, WA

The authors declare no conflicts of interest.

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In patients with iron deficiency without anemia, does iron treatment improve outcomes?

EVIDENCE-BASED ANSWER

Treating iron deficiency even in the absence of anemia improves functional outcomes and quality of life in patients with systolic heart failure (HF) (strength of recommendation [SOR]: **B**, meta-analysis of randomized controlled trials). It also improves symptoms in premenopausal women with fatigue (SOR B: randomized placebo-controlled single-blinded study).

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A 2016 meta-analysis of randomized controlled trials (N=767) evaluated the effects of intravenous (IV) iron

therapy on mortality, hospitalization, quality of life, and HF symptoms in iron-deficient patients with systolic HF.[1] Five trials fulfilled the inclusion criteria of at least a single blind, randomized, controlled trial in patients with left ventricular ejection fraction (LVEF) of ≤45% who received IV iron therapy (iron sucrose or ferric carboxymethalose) without erythropoiesis-stimulating agents. In total, there were 851 patients with systolic HF and iron deficiency, 509 of whom were treated with IV iron therapy. IV iron therapy was typically provided at 200 mg weekly until repletion occurred, then maintenance every four weeks for up to 24 to 52 weeks, depending on the study. Mean iron total dose ranged between 1,000 and 1,850 mg. Key end points included clinical events such as all-cause death, cardiovascular death, and HF hospitalization. Additional end points included change in baseline on various quality of life scoring questionnaires, change in New York Heart Association (NYHA) functional class (ranging 1–4, with class 1—no limitation during ordinary activity, class 4—inability to carry out any physical activity), 6-minute walk test (total distance walked in 6 minutes as a measure of physical function, with minimally important difference with interventions a difference of 30 m), and LVEF. Subgroup analysis of patients with systolic HF who were treated with IV iron in the absence of anemia (176 total patients) showed reduced incidence of combined all-cause death or cardiovascular hospitalization (odds ratio [OR], 0.51; 95% CI, 0.27–0.97). A trend toward reduced cardiovascular death or hospitalization for worsening HF (OR, 0.46; 95% CI, 0.20–1.03), and HF hospitalization (OR, 0.41; 95% CI, 0.15–1.14) did not reach statistical significance. No difference was found between treatment and all-cause or cardiovascular death alone. For the additional end points of a 6-minute walk test, NYHA class, and LVEF, the mean difference (MD) was calculated between a value at the end of the study and the baseline value. The 6-minute walk test improved (30.8 m; $P<.0001$) as well as the NYHA class (−0.54; $P<.0013$) in the pooled treatment groups, with similar findings in the subgroup analysis of patients without anemia. No significant change in LVEF was found. Because these studies were not specifically powered for the nonanemic patients, there is a risk for a type II error (false-negative), and some improvements may not have been detected as a result of an inadequate sample size.

A 2014 randomized, placebo-controlled single-blinded, comparative, superiority study (n=294) evaluated change in fatigue symptoms and quality of life with iron supplementation in patients with iron deficiency and no anemia. The study included nonpregnant premenopausal women of ≥18 years of age in Europe with iron deficiency (ferritin <50 μg/L with low transferrin saturation or ferritin <15 μg/L) of unknown etiology with normal or borderline hemoglobin. Exclusions included other concurrent medical conditions, such as major depressive disorder, sleep disorder, or chronic inflammatory disease.[2] Patients received either one single infusion of ferric carboxymaltose (FCM) or a placebo. Hematology and iron status were evaluated at days seven, 28, and 56, and fatigue symptoms were assessed at each visit with a 22-item Piper Fatigue Scale (PFS), which uses a scale from 1 to 10 (1–3 none or mild, 4–6 moderate, 7–10 severe). Additionally, an SF-12 quality of life (QoL) questionnaire and a computerized cognitive test assessing attention, concentration, and short-term memory were obtained at the start of treatment and day 56. The SF-12 QoL questionnaire employs a numeric or yes/no scale with questions targeting how often and to what extent symptoms interfered with daily physical and mental functioning. The primary end point was the proportion of patients with a decrease in one or more points in total PFS score from baseline to day 56. Iron infusions reduced PFS scores by 50% or more compared with placebo at day 56 (33.3% vs 16.4%; $P<.001$; number needed to treat [NNT]=5.9); More patients in the FCM group reached the primary end goal of decreasing one or more on the PFS (65.3% vs 52.7%; $P=.03$; NNT=8.0). Changes in cognitive function were numerically larger, but there was no statistical difference between the FCM and placebo-treated groups. With regard to the SF-12 QoL questionnaire, there was a self-reported improvement in mental health (MD, 3.0; 95% CI, 0.9–5.2; $P=.007$) but no improvement in physical health. Limitations of the study included potential compromised blinding (dark stools and constipation in treatment group), and iron treatment given as a one-time IV treatment. EBP

Elizabeth Maldonado, MD
Amelia Buttolph, MD
Camp Lejeune Family Medicine Residency
Camp Lejeune, NC

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Do antacids before cesarean delivery reduce the risk of aspiration pneumonitis?

EVIDENCE-BASED ANSWER

No patient-oriented evidence is available. Pretreatment with a combination of soluble antacids and H2-receptor antagonists, H2-receptor antagonists alone, and proton pump inhibitor alone all reduce the theoretical risk of aspiration pneumonitis by raising gastric pH and without increasing volume (SOR: **C**, meta-analysis of randomized controlled trials with disease-oriented outcomes). National surgical and anesthesia guidelines recommend administration of both soluble antacids and H2-receptor antagonists before cesarean section to reduce the risk of aspiration pneumonitis (SOR: **C**, evidence-based and consensus-based guidelines for disease-oriented outcomes).

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A 2014 systematic review and meta-analysis of 16 randomized controlled trials (RCTs; N=1,811) of pregnant women undergoing cesarean delivery examined the effectiveness of soluble antacids, H2-receptor antagonists, or proton pump inhibitors (PPIs) to decrease the risk of aspiration pneumonitis.[1] The RCTs examined numerous soluble antacids, H2-receptor antagonists, and PPIs, including sodium citrate/nitrate, magnesium trisilicate, Mylanta, Gelusil, cimetidine, ranitidine, nitazidine, and omeprazole. Medications were administered at typical dosages. Preoperative administration times ranged from the night before to immediately after cesarean delivery. These medications were compared with no treatment, placebo, and each other. When specified, pregnancy gestation ranged from 36 weeks to full term. Anesthesia was general in over 70% of cases, although cesarean delivery were more commonly elective than emergent. Though identified as the primary outcomes in this meta-analysis, no available RCTs examined the incidence, morbidity, or mortality of aspiration pneumonitis. Disease-oriented primary outcomes included low gastric pH (<2.5) and elevated gastric volume (>0.4 mL/kg), measured after induction of anesthesia, typically by aspiration via gastric tube. Although not a prespecified outcome and not validated, most RCTs also reported the theoretical risk of aspiration, a composite score based on gastric pH and volume. Soluble antacids, H2-receptor antagonists, and PPIs substantially reduced the incidence of gastric pH <2.5 when compared with placebo or no treatment (see **TABLE**). H2-receptor antagonists and PPIs also decreased the theoretical risk of aspiration, though soluble antacids did not. The combination of soluble antacids with H2-receptor antagonists was associated with a lower theoretical risk of aspiration when compared with placebo, soluble antacid, or PPI alone. Limitations of this meta-analysis include heterogeneous RCT design, lack of patient-oriented outcomes, predominate use of general anesthesia, use of an unvalidated scoring system, and high risk of bias because of multiple instances of failing to report allocation process, blinding, or attrition.

The 2018 Enhanced Recovery After Surgery Society recommended administration of both soluble antacids and H2-receptor antagonists before cesarean delivery to decrease the risk of aspiration pneumonitis.[2] Evidence for this guideline was based on the previously cited review; it cited a low level of evidence (further research is very likely to impact the estimated effect) but strong recommendation grade (desirable effects clearly outweigh the undesirable effects).

TABLE. Comparison of acid therapies before cesarean delivery to reduce gastric pH and theoretical risk of aspiration pneumonitis[1]

Intervention/comparison	Total number of studies and patients	Gastric pH<2.5 RR (95% CI)	Theoretical risk of aspiration RR (95% CI)[a]
Soluble antacid vs. placebo/none	3 trials N=168	**0.17 (0.09–0.32)** 2 trials, N=108	0.07 (0.00–1.04) 1 trial, n=22
H2 blocker vs. placebo/none	6 trials N=385	**0.09 (0.05–0.18)** 2 trials, N=170	**0.07 (0.01–0.33)** 4 trials, N=255
PPI vs. placebo/none	2 trials N=130	**0.26 (0.14–0.46)** 1 trial, n=80	**0.14 (0.03–0.74)** 2 trials, N=130
H2 blocker and soluble antacid vs. placebo/none	1 trial n=89	**0.02 (0.00–0.15)** 1 trial, n=89	Not reported
Soluble antacid vs. H2 blocker	4 trials N=175	**0.07 (0.01–0.52)** **2 trials**, N=**135**	1.00 (0.18–5.5) 1 trial, n=16
H2 blocker vs. PPI	4 trials N=332	**0.39 (0.16–0.97)** **1 trial**, n=**120**	0.93 (0.2–4.4) 4 trials, N=323
Soluble antacid and H2 blocker vs. soluble antacid alone	2 trials N=714	**0.12 (0.02–0.92)** **1 trials**, n=**119**	**0.11 (0.03–0.46)** **1 trial**, n=**595**
Soluble antacid and H2 blocker vs. PPI	1 trial n=109	Not reported	**0.12 (0.20–0.91)** **1 trial**, n=**109**
H2 blocker and PPI vs. PPI alone	1 trial n=113	Not reported	0.33 (0.10–1.3) 1 trial, n=113

Bolded items are statistically significant values. [a] Although the risk of gastric volume >0.4 mL/kg is used to calculate theoretical aspiration risk, it was not explicitly reported in most RCTs, and is thus omitted from this table. PPI = proton pump inhibitor; RCT = randomized controlled trial.

The 2016 American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology also recommended administration of soluble antacids and H2-receptor antagonists before cesarean delivery to decrease the risk of aspiration pneumonitis.[3] This recommendation was based on RCTs showing increased gastric pH with medical treatment. This joint society guideline was consensus based; it cites level A2-B evidence (multiple RCTs with benefit, but insufficient to conduct a viable meta-analysis). EBP

Brianne H. Rowan, MD, MPH
Joseph Angel, MD
Tacoma Family Medicine, Tacoma, WA

The authors declare no conflicts of interest.

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What is the best tubal interruption technique to use during cesarean delivery?

EVIDENCE-BASED ANSWER

Not clear. Salpingectomy and standard bilateral tubal ligation have similar complication rates (SOR: **A**, consistent results from 2 randomized controlled trials [RCTs]), but which procedure is faster remains unclear (no SOR, conflicting evidence from 2 RCTs). Complication rates for Falope Ring application and modified Pomeroy method are similar; however, Falope Ring application is an easier procedure to perform and less time-consuming (SOR: **B**, single RCT).

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A 2018 randomized controlled trial (RCT; n=44) examined the difference in operating time and complication rates of salpingectomy versus standard tubal ligation for sterilization at the time of cesarean delivery in women 21 years old or older.[1] Patients with placenta accreta, a congenitally or surgically absent fallopian tube, required cesarean delivery after experiencing labor, or a known hereditary cancer syndrome were excluded. Participants were randomized into Pomeroy or Parkland method (n=18; surgeon preference) or salpingectomy (n=19). The primary outcome measured was sterilization procedure time with the noninferiority margin set at five minutes. Salpingectomy was noninferior compared with tubal ligation (5.6 vs 6.1 minutes, $P<.05$). No differences were noted between salpingectomy and tubal ligation in median total operating time (60 vs 68 minutes, $P=.34$) or estimated blood loss (600 vs 700 mL, $P=.09$).

A 2017 RCT (n=80) evaluated salpingectomy compared with standard bilateral tubal ligation at the time of cesarean delivery in women with undesired fertility.[2] Patients (mean age 33 years old) were excluded if the maternal age was less than 25 years old, a prenatal fetal anomaly was diagnosed, or they had a history of tubal surgery. Patients were randomized to either standard bilateral tubal ligation (n=40) or bilateral salpingectomy (n=40). Modified Pomeroy and Parkland methods were used in rare situations. The primary outcomes measured were the total operative time and successful bilateral completion of the sterilization procedure (skin incision to skin closure). Secondary outcomes measured were estimated blood loss and complications up to six weeks after delivery. Total operative time was significantly longer for the salpingectomy group compared with the tubal ligation group (75 vs 60 minutes, $P<.01$). Successful completion of bilateral salpingectomies was significantly higher compared with bilateral tubal ligations (95% vs 68%, $P<.01$). No significant differences were noted between salpingectomy and tubal ligation groups in complications (18% vs 15%, $P=.76$) and estimated blood loss (1,007 vs 930 mL, $P=.56$). However, a slightly shorter maternal hospital stay was associated with the salpingectomy group (3.4 vs 3.9 days, $P=.02$).

A 2015 RCT (n=500) evaluated failure rates, complications, and technical difficulties of the Falope Ring application for tubal ligation compared with modified Pomeroy's technique at the time of cesarean delivery.[3] Patients were second gravida or more and at term gestation. Women reporting any maternal or fetal contraindications for tubal sterilization were excluded. Participants were randomized to either tubal sterilization by Falope Rings (n=250) or modified Pomeroy's technique (n=250). No significant difference was noted in failure rates between Falope Rings and the modified Pomeroy technique of tubal occlusion (0% vs 0.04%, $P>.05$). Falope Ring application did have a significantly lower rate of complications compared with modified Pomeroy's technique (2.8% vs 8%, $P<.01$) and lesser mean duration of application (20 seconds vs four minutes, $P<.01$). Three patients underwent tubal recanalization in both groups because of neonatal deaths. One patient from either of the groups conceived. EBP

Socorro Shelton, MD
Charelle O Smith, MD
Southern Illinois University Family Medicine
Carbondale, IL

The authors declare no conflicts of interest.

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In healthy women at low risk of complications, does water immersion in first stage of labor decrease the number of women receiving epidural anesthesia?

EVIDENCE-BASED ANSWER

Yes. In low-risk laboring women, water immersion in the first stage of labor is a safe intervention that decreases epidural anesthesia use with a number needed to treat (NNT) of 26 (SOR: **A**, meta-analysis of consistent randomized controlled trials). Water immersion should be offered to reduce use of epidural anesthesia and is a safe procedure (SOR: **C**, consensus guideline).

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A 2018 meta-analysis of 15 randomized controlled trials (RCTs; N=3,663) evaluated the effect of water immersion during labor on maternal and neonatal outcomes.[1] Patients were low-risk laboring women (nulliparous and multiparous) at term gestation with a singleton fetus. A subanalysis of five RCTs (N=2,349) specifically evaluated the effect of water immersion versus no water immersion during the first stage of labor on regional anesthesia. Four of the five trials specified epidural use. (It was not clear if the fifth trial [n=33] used epidurals or another forms of regional anesthesia.) The intervention group underwent water immersion during the first stage of labor, defined by complete submersion of the pregnant abdomen in water ranging from 37 to 39°C. The control group did not undergo water immersion at any stage of labor. Pooled results of the five trials demonstrated reduced use of regional anesthesia for women using water immersion compared with those without water immersion (risk ratio 0.91; 95% CI, 0.83–0.99; NNT=26). No increase in fetal or maternal adverse outcomes were observed in the water immersion group. Limitations of this study included universal absence of blinding, one study with selection bias, and three studies with high risk of attrition bias.

A 2016 evidence-based guideline (largely based on the original meta-analysis referenced above) statement from The American College of Obstetricians and Gynecologists recommended offering water births to healthy women with uncomplicated term pregnancies.[2] The guideline stated that immersion in water during the first stage of labor may decrease use of epidural analgesia and is a safe procedure overall (no strength given). EBP

Anne Gair, MD
Javad Keyhani, MD
University of Minnesota Medical Center FMR
Minneapolis, MN

The authors declare no conflicts of interest.

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In women who are pregnant and smoke, does nicotine replacement therapy (vs no pharmacological treatment) affect the rate of birth defects?

EVIDENCE-BASED ANSWER

Pregnant women who smoke and use nicotine patches for smoking cessation do not have more newborns with congenital anomalies, respiratory issues, or developmental impairments compared with placebo (SOR: **B**, single randomized controlled trial). Major congenital anomaly rates are similar between infants born to pregnant smokers treated with nicotine replacement therapy, pregnant smokers without treatment, and nonsmokers (SOR: **B**, single cohort trial).

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A 2014 multicenter, randomized, double-blind, placebo-controlled trial (N=1,050) examined the effect of nicotine patches on infant and maternal outcomes at two years.[1] Pregnant women (16–45 years old) who smoked at least five cigarettes per day between 12 and 24 weeks gestation and with an inhaled carbon monoxide level of greater than or equal to eight ppm were randomized to receive eight weeks of nicotine patches (n=521) dosed at 15 mg per 16 hours or placebo (n=529). Data for congenital anomalies were gathered at the time of birth. At 24 months, participants (or their physician) also answered a questionnaire about behavioral or developmental impairment. The questionnaire was adapted from the Ages and Stages Questionnaire Third Edition and assessed the following five domains: communication, gross motor, fine motor, problem solving, and personal and social development. Additional questions also assessed general and specific parental concerns about infant development. The cumulative score for each domain stratified children into three categories indicating high, borderline, or low risk for developmental impairment. Infants who scored in one or more high-risk zones for any domain were defined by the investigators as having a definite developmental impairment. Suspected developmental impairment was defined by scores in the borderline range. No difference was noted between the nicotine replacement therapy (NRT) and placebo groups in rates of congenital anomalies. Infants born to mothers who used NRT were more likely to present at 24 months without any behavioral or developmental impairment compared with those in the placebo group (73% NRT vs 65% placebo; OR 1.40; 95% CI, 1.05–1.86). Incidence of definite developmental impairments did not differ. Secondary analysis demonstrated that pregnant women who used NRT patches for 11 to 56 days were more likely to have children with no impairment than those who used NRT for 1 to 10 days (OR 1.72; 95% CI, 1.2–2.5). Data regarding amount of maternal smoking were not available for analysis, which may have provided additional information regarding dose-response effect of the study intervention.

A 2015 population-based cohort (n=192,498) evaluated the safety of using NRT for smoking cessation in pregnancy.[2] Pregnant women (15–49 years old) with live births between January 2001 and December 2012 were categorized into the NRT group (n=2,677), smoker group (n=9,980), and control group (n=179,841). All the pregnant women were selected from The Health Improvement Network (THIN), an anonymized database that is representative of the UK population-at-large. Information on children with major congenital anomalies (MCAs) was extracted from THIN. Women who were prescribed NRT during their first trimester or within four weeks before estimated conception were placed in the NRT group. Women who were smokers and did not receive a prescription for NRT were placed in the smoker group. The control group consisted of nonsmokers or ex-smokers for at least three years. Pregnant women whose smoking status was missing were excluded. The primary outcome was cumulated data of all MCAs. Observed MCAs (n=5,355) included the heart, limb, genital system, urinary system, orofacial cleft, respiratory system, digestive system, and various others. No difference was noted in absolute risk of all combined MCAs between the study groups. The NRT group had a higher risk of respiratory system abnormalities compared with the control group (OR 4.65; 99% CI, 1.76–12.2) and smoker group (OR 3.49; 99% CI, 1.05–11.62). Of note, only 10 cases (3 per 1,000 live births) of respiratory system anomalies in the NRT group were limited, limiting clinical significance. No other differences in MCAs were noted between the NRT group versus the control group. A limitation of this study was that the investigators did not provide the formulation, dose, or duration of NRT. The low use of NRT in pregnancy limited the statistical power of this comparison. Researchers did not report pack-year history for the pregnant women in the smoker group. EBP

Cassidy B. Williams, PharmD, BCPS
Allison Flaherty, DO
Gretchen Shelesky, MD, MS
UPMC St. Margaret, Pittsburgh, PA

The authors declare no conflicts of interest

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Is fenugreek effective at increasing breast milk production?

EVIDENCE-BASED ANSWER

Fenugreek supplementation may increase breast milk production compared with placebo (SOR: **B**, meta-analysis of small randomized controlled trials [RCTs] and single RCT) but performs worse than other supplements and pharmaceutical galactagogues (SOR: **B**, meta-analysis of small RCTs). Fenugreek supplements are not recommended because of the lack of standardization protocols and potential for hypersensitivity reactions (SOR: **C**, expert opinion).

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A meta-analysis of five randomized controlled trials (RCTs) analyzed the effectiveness of fenugreek as a galactagogue in lactating mothers.[1] Patients were 20 to 40 years old, 1 to 7 days postpartum, and were from Middle Eastern Europe, Africa, and the United States. Those in the treatment groups received fenugreek via tea, powder, or capsules with dosing ranging from 575 mg to 7.5 g. Comparator groups were given placebo, palm dates, usual care, or *Coleus amboinicus* leaves. Total treatment and follow-up was a median of 60 days. All breast milk volumes were converted to milliliters per feed. Fenugreek was noted to have superior efficacy to placebo (4 trials; N=164; weighted mean difference [WMD] 11.1; 95% CI, 6.7–15.6) as well as to all control arms (4 trials; N=164; WMD 17.8; 95% CI, 11.7–23.9) for breast milk volume. However, fenugreek was inferior to both *C amboinicus* leaves (1 trial; n=22; WMD –15.0; 95% CI, –16.9 to –13.1) and palm dates (1 trial; n=25; WMD –14.6; 95% CI, –24.1 to –5.2).

A 2018 RCT of 50 exclusively breastfeeding mothers examined the effects of an herbal supplement containing fenugreek, ginger, and turmeric on breast milk volume over four weeks.[2] Participants were a mean age of 25 years old, were one month postpartum, and were exclusively breastfeeding. Mothers were excluded if they had a chronic disease, were currently smoking or drinking, or if they birthed twins. Women were given a supplement three times a day containing 200 mg fenugreek, 120 mg ginger, and 100 mg turmeric (n=25), or a similar appearing supplement containing corn starch (n=25). Mothers used a manual breast pump for two days and recorded the volume at the start of the trial and then at two and four weeks. A significant increase in breast milk volume was noted from baseline in the supplement group compared with the placebo group at two weeks (49% vs 11%, $P<.05$) and at four weeks (103% vs 24%, $P<.05$). A significant difference was not observed in energy or nutrient composition of the milk or in diet between groups.

A 2018 evidence-based guideline from the Academy of Breastfeeding Medicine did not make a recommendation about herbal supplementation but cautions about their use due to lack of regulation and insufficient evidence of efficacy and safety (Strength: 11A–11B, mixed results from mostly low-quality studies).[3] Additionally, reviewers expressed concerns regarding the lack of standardization in preparations and oversite for products available in the United States, as well as specific reports of severe allergic reactions to fenugreek, which can include wheezing, loss of consciousness, skin rash, asthma, and possible anaphylaxis. EBP

Britain Parrish, MD
Garth Brand, MD
Montana Family Medicine Residency, Billings, MT

The authors declare no conflicts of interest.

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Do topical vaginal estrogens help prevent rUTI in postmenopausal women?

EVIDENCE-BASED ANSWER

It appears likely that topical estrogens reduce urinary tract infection (UTI) frequency in older women with a history of frequent UTIs (SOR: **B**, randomized controlled trials). Vaginal estrogens are recommended to prevent recurrent UTI in postmenopausal women (SOR: **C**, consensus guideline).

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A 2016 systematic review of nine randomized controlled trials (RCTS; N=1,028) evaluated pharmacologic interventions in the prevention of urinary tract infection (UTI) in patients with recurrent UTI (rUTI) in community-dwelling postmenopausal women.[1] Patients were excluded if any had a spinal cord injury, self-intermittent catheters, chronic indwelling catheters, dementia, or surgery within 30 days. Researchers define rUTI as three or greater diagnosed UTIs in 12 months or two UTIs in six months. Two trials (N=201) specifically evaluated topical vaginal estrogen. One trial evaluated 0.5 mg of estriol vaginal cream nightly (n=50) for two weeks followed by twice weekly for eight months compared with placebo cream (n=43) used in the same manner in postmenopausal women (mean age, 65 years). Compared with placebo, patients in the estrogen group experienced significantly fewer UTIs per year (0.5 vs 5.9; $P<.001$). Adverse reactions reported included vaginal irritation, burning, or itching. The second trial (n=108; mean age, 79 years) evaluated 2-mg estradiol vaginal ring placed every 12 weeks for nine months versus placebo. UTI recurrence was defined as symptoms and/or positive nitrates plus positive culture. The incidence of UTI was reduced in the estrogen group versus placebo (51% vs 80%; no *P* value provided).

A 2019 multicenter, single-blinded RCT (n=35) examined the effectiveness of vaginal estrogen for the prevention of rUTI in postmenopausal women.[2] Women were included if experiencing a UTI three times or more per year or two in six months. Patients with urologic surgery within three months or surgery planned within one year, diagnosis of painful bladder syndrome, history of UTI requiring treatment based on allergies or bacteria resistance profiles were excluded. The mean age was 73 years in the estrogen group (n=18) and 68 years in the placebo group (n=17). The treatment group received either conjugated estrogen cream (0.312 mg vaginally twice weekly at night) or estradiol ring (2 mg vaginally every 3 months placed by study personnel) for six months, whereas the control group received placebo cream. If a patient developed three UTIs within the six-month study period, unblinding was conducted, and patients were switched from placebo to the treatment group. The primary outcome was the occurrence of UTI defined as urinary symptoms with positive culture at six months, or at the end of study blinding, whichever occurred first. Adherence was defined as tube weights within 20% of expected weight or presence of estrogen ring. The final analysis included 26 participants as one dropped before the initiation of treatments, six dropped out of the placebo group, and three dropped from the treatment group for unspecified reasons. Intent-to-treat analysis demonstrated significantly lower incidence of UTI with vaginal estrogen compared with placebo (50% vs 94%; $P=.04$). As-treated analysis found significantly lower UTI incidence with vaginal estrogen versus placebo (53% vs 91%; $P=.04$). However, patients treated with estrogen cream only did not have a significant difference in UTI recurrence compared with placebo (71% vs 91%; $P=.48$). All participants in the estrogen ring group were adherent and had significantly lower rates of UTI compared with placebo (38% vs 91%; $P=.04$). No adverse events were observed related to drug therapy.

A 2019 evidence-based guideline from the American Urological Association recommended that peri- and postmenopausal women with rUTIs receive vaginal estrogen therapy to reduce risk of rUTI (moderate recommendation, grade B evidence level).[3] EBP

Paul Bucolo, MD
Julia Horton-Bertrand, MD, MPH
Lois Coulter, PharmD, BCPS
Jonell Hudson, PharmD, BCPS
Ronald Brimberry, MD
UAMS Northwest FMR, Fayetteville, AR

The authors declare no conflicts of interest.

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Does cranberry extract taken daily by mouth prevent rUTIs in adult women

EVIDENCE-BASED ANSWER

Maybe. Cranberry extracts may reduce recurrent urinary tract infections (rUTIs) in women by 50% to 70% (SOR: **C,** systemic reviews of lower-quality randomized controlled trials). Cranberry extract use results in little to no harm and may be offered as a prophylaxis for rUTI in women (SOR: **C,** clinical guideline).

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A 2017 meta-analysis of seven randomized controlled trials (RCTs; N=1,498) evaluated the efficacy of cranberry products for the reduction of recurrent urinary tract infections (rUTIs).[1] A subanalysis of two trials (N=282) specifically evaluating the effectiveness of cranberry extract was identified. Patients had a mean age of approximately 40 years, were free of UTI as baseline but had been diagnosed with two or more symptomatic UTIs in the past 12 months, and were not pregnant. Both trials excluded patients with anatomical anomalies, which could have altered the incidence of UTIs, diabetes treated with insulin, and those with immunosuppression. One trial (n=182) evaluated 500 mg of cranberry fruit powder capsules twice daily for six months or placebo. The second trial (n=100) evaluated two concentrated cranberry juice tablets (no dose provided) twice daily for 12 months. Pooled cumulative incidence of rUTI in patients receiving cranberry extract was significantly reduced compared with placebo (risk ratio [RR], 0.48; 95% CI, 0.29–0.79). Adverse events did not differ between treatment and placebo in either study. Limitations included lack of standardization of cranberry extract dose or strength.

A 2012 systematic review of 24 RCTs (N=4,473) evaluated the use of cranberry products in the prevention of rUTIs.[2] Two RCTs compared cranberry in tablet or powdered forms with placebo. One trial was already summarized and pooled above. The remaining trial is summarized below. A 2011 RCT (n=60) evaluated cranberry powder for the prevention of rUTI in nonpregnant women of ages 18 to 40 years with rUTI and culture-positive UTI at baseline. Patients were excluded if they had antibiotics within 48 hours, urinary catheter within previous two weeks, diabetes, cardiovascular disease, or history of pyelonephritis or kidney stones. The treatment group received 500 mg (n=21) or 1,000 mg (n=23) of tablet-form cranberry daily for 90 days, whereas the control group (n=16) received placebo. Primary outcome was symptomatic culture-proven rUTI. Results combined the two treatment dosage groups and found that rUTI occurred in 10% of the treatment group and 31% of the placebo group (RR, 0.31; 95% CI, 0.07–1.5). Adverse events did not differ between treatment and placebo in either study.

The 2019 American Urological Association, Canadian Urological Association and the Society of Urodynamic Female Pelvic Medicine, and Urogenital Reconstruction evidenced-based, clinical practice guideline stated that cranberry may be considered as prophylaxis in rUTIs (Evidence Level C; no apparent net benefit or harm).[3] This guideline defined rUTI as two episodes of acute bacterial cystitis within six months or three episodes within one year. EBP

Emmanuel Obi, MD
Katharine Darland, MD, MBA
Jonell Hudson, PharmD, BCPS
Lois Coulter, PharmD, BCPS
Edward Yang, MD
University of Arkansas for Medical Sciences
Northwest FMR, Fayetteville, AR

The authors declare no conflicts of interest.

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Is a clinical breast examination useful for screening for breast cancer?

EVIDENCE-BASED ANSWER

It depends. The clinical breast examination is not useful in low-risk women already receiving mammograms and increases false-positive rates (SOR: **B**, based on a systematic review of three randomized controlled trials [RCTs], one case-control, and 3 large cohort studies). However, clinical breast examinations should be offered to women who are not receiving mammograms (SOR: **C**, expert opinion).

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A 2015 systematic review of 90 various studies (N=5,635,301) examined the benefits and harms of breast cancer screening using mammography and clinical breast examinations.[1] Patients in these studies were 20 years old and older with and without risk factors for breast cancer. A meta-analysis was not completed on the data because no updated evidence was discovered. A subset of three RCT=randomized controlled trials, three cohorts, and one case-control study (N=520,413) focused on the use of clinical breast examination was identified. A large RCT (n=62,000) randomized women to either mammography, clinical breast examination, or a control group of no screening and measured case-fatality rates over a period of nine years. After nine years, mammography testers had lower fatality rates than both clinical breast examination alone and the control group (14% vs 32% vs 47%, respectively; $P<.01$). A case-control study (n=3,852) compared clinical breast examination with no screening in a sample of 71% "average-risk" and 19% "high-risk" women over three years. Breast cancer mortality with clinical breast examination compared with no screening showed no significant difference (odds ratio 0.94; 95% CI, 0.79–1.12). Two large North American cohorts (N=351,918) examined the addition of clinical breast examination to mammography. Both found that the addition led to an overall increase in false-positive rate, with an estimated 55 false positives per additional breast cancer detected. The remaining trials and cohorts also demonstrated no improvements with clinical breast examination. One notable limitation was that the first trial reported case fatality rather than mortality, making it susceptible to lead time bias.

The 2016 United States Preventive Services Task Force released an evidence-based guideline, concluding insufficient evidence exists to assess the additional benefits or harms for clinical breast examination beyond mammography for breast cancer screening (I Statement, insufficient evidence).[2] This was notably not updated from the previous 2009 recommendation. The statement further stated that indirect evidence suggested that if clinical breast examination is the only screening test available, it may detect a substantial proportion of cases of cancer (I Statement, insufficient evidence).

A 2017 evidence-based practice bulletin from the American College of Obstetrics and Gynecology recognized the uncertainty of the additional benefits of clinical breast examination and recommended it be offered through shared decision-making every one to three years for women aged 25 to 39 years old and annually for women 40 years old and older.[3] EBP

Jacquelyn Cameron, MD
Timothy Ramer, MD
Family Medicine Program
University of Minnesota Medical Center
Minneapolis, MN

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Does providing opiate maintenance therapy during incarceration increase participation in community treatment programs after release?

EVIDENCE-BASED ANSWER

Yes. Opiate maintenance therapy (MAT) during incarceration does increase participation in community substance use treatment programs following release (SOR: **A,** meta-analysis of randomized controlled trials [RCTs] and quasi-RCTs). MAT treatment with buprenorphine results in better participation and intention to continue treatment rates compared with methadone (SOR: **B,** RCT).

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A 2017 meta-analysis of eight randomized controlled trials (RCTs), five secondary-analyses of RCTs, and 11 quasi-experimental studies (N=807) evaluated the efficacy of maintenance therapy (MAT) on various behavioral outcomes in incarcerated individuals.[1] Participants were majority incarcerated men with opioid addiction started on methadone, naltrexone or buprenorphine treatment (unspecified dosages). Control groups were passive referral to treatment upon release from prison because this is the standard of care for opioid use among correctional facilities in the United States. Total follow-up in most trials was between one and six months, with one trial following for four years. Incarcerated individuals treated with methadone were significantly more likely to participate in community treatment upon release compared with those without treatment (3 trials; N=807; odds ratio, 8.7; 95% CI, 2.5–31).

A 2009 RCT (n=116) compared the effectiveness of buprenorphine or methadone treatments on follow-up maintenance treatment in a community setting.[2] Participants were heroin-dependent, adult men between 18 and 65 years, not enrolled in community methadone treatment, and sentenced to 10–90 days in jail. Inmates who had taken nonprescribed "street" methadone within three days, who received more than 20 mg/d of prescribed methadone, or those with HIV infection were excluded. Participants were randomly assigned either to buprenorphine (n=60) or methadone maintenance (n=56). Inmates in the methadone treatment group were initiated with 30 mg/d subsequently stepped up to a maximum of 70 mg/d, whereas those in the buprenorphine treatment group received an initial dose of 4 mg, which could be stepped up to a maximum of 32 mg. Participants were then qualitatively interviewed about their stated intention to continue treatment, and their attendance rates at postrelease community treatment centers were collected. All subjects who received either buprenorphine or methadone were eligible for a three-month postrelease interview to follow-up on their progress. Buprenorphine and methadone maintenance completion rates in jail were equally high (82% and 75%, respectively; $P>.05$), but the buprenorphine group reported postrelease treatment in the community significantly more often than the methadone group (48% vs 14%; $P<.001$). Before release, a survey of buprenorphine patients indicated that they intended to continue treatment after release more often than methadone patients (93% vs 44%; $P<.001$). After initiating MAT in jail, those in the buprenorphine treatment group expressed an increased interest, willingness, and intention to continue buprenorphine after release. No serious adverse events were observed or reported by subjects during the course of the study. A key limitation was that methadone-assigned patients may have received suboptimal doses of methadone. EBP

Ahmad Abdl-Haleem, DO
Mary R. Talen, PhD
Northwestern Family Medicine Residency Program
Chicago, IL

The authors declare no conflict of interest.

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