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# EVIDENCE-BASED PRACTICE

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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.*

## Your brain . . . on media campaigns

Recently I was wandering through the Washington State Museum of History and Industry when I came upon an installation about cannabis attitudes and laws. In 1 corner of the display, the curators were showing *Reefer Madness*, a 1936 antidrug propaganda film. I had to watch only a few scenes to understand why the movie became something of a laughing stock. At a minimum, the acting was horrible.

*Reefer Madness* was released before my time. But I do vividly recall a later antidrug media campaign that focused on eggs. The TV announcer showed an egg and said, "This is your brain." The announcer broke the egg into a frying pan and said, "This is your brain on drugs." The educational message was not particularly scientific and I suspect the American Egg Board (www.aeb.org) really hated it.

Recently, a group of researchers, noting that a single antidrug media campaign had cost US taxpayers $2.7 billion over 10 years, decided to run a meta-analysis on the effectiveness of such efforts.[1] They included 19 studies with nearly 185,000 participants. Evaluating just the RCTs of experimental studies showed no evidence that mass-media campaigns modified use of illicit drugs (5 trials, n=5,470; standardized mean difference [SMD] –0.02; 95% CI, –0.15 to 0.12).

In field studies, outcomes were more varied and difficult to combine. Several interventions actually resulted in an increased use of marijuana and, in 1 instance, LSD. Five studies on a campaign against methamphetamine use (n=26,273) showed no change in "past month" use in kids 12 to 17 years old (odds ratio [OR] 1.16; 95% CI, 0.83–1.61), but some reduction in "past year" use (OR 0.59; 95% CI, 0.43–0.81).[1] Other outcomes were comparably conflicted and muddy.

Our nation's public health folks got it right when educating the public about the importance of seat belts and the dangers of cigarettes,[1] so I know we can do a better job here. Because spending another $2.7 billion and not getting any benefit from it certainly fits every citizen's definition of madness.

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### REFERENCE

1. Allara E, Ferri M, Bo A, Gasparrini A, Faggiano F. Are mass-media campaigns effective in preventing drug use? A Cochrane systematic review and meta-analysis. *BMJ Open*. 2015; 5:e007449.







### 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.

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# Do the food choices available in your neighborhood influence your BMI?

## EVIDENCE-BASED ANSWER

They may. Living in areas with less healthy food options or a higher density of small food stores with a poor ratio of healthy food to junk food is associated with a higher risk of obesity. Having more large food supercenters nearby is associated with a decreased prevalence of obesity. People living or shopping in a lower socioeconomic status area generally have a higher body mass index (BMI) (SOR: **B**, cross-sectional studies).

## Evidence summary

A 2012 cross-sectional study of 1,302 low-income adults in Louisiana examined the association between BMI and access to supermarkets (defined as sales of >$5 million per year) and small food retailers.[1] Urban areas (>2,000 people per square mile) in southeast Louisiana were used for data collection, gathered using both in-store surveys and telephone surveys.

Individuals living in areas with more healthy food options (fresh, canned, and frozen fruits and vegetables) compared with junk food (high-calorie, low-nutrient foods including candy, chips, cookies, pastries, and soda) were less likely to be overweight (relative risk [RR] 0.55; 95% CI, 0.33–0.91) or obese (RR 0.50; 95% CI, 0.30–0.83). People living in an area with a higher density of small food stores had a higher risk of obesity (RR 1.1; *P*=.02; CI not given). However, when adjusted for the ratio of healthy food to junk food options available, the number of small food stores within a defined radius of respondents' homes had no effect on the incidence of obesity (RR 0.99; 95% CI, 0.99–1.0).[1]

A cross-sectional study from 2011 evaluated obesity rates among adults using the US Department of Agriculture Economic Research Service Food Atlas, an interactive online tool.[2] The study investigated the association between access to farmer's markets, grocery stores, and supercenters and obesity prevalence in 3,141 counties (total number of residents not given).

In both metro and nonmetro counties, an increase in 1 standard deviation in the number of supercenters per 1,000 residents decreased obesity prevalence by 0.08%.[2]

A 2006 cross-sectional study of adults (N=2,144) used random household surveys in lower socioeconomic status areas of Los Angeles to examine the correlation of shopping habits and food retailer availability with BMI and obesity rates.[3] Socioeconomic status designation (very low, low, high, very high) was derived from a standardized disadvantage score based on 4 factors (percent living below poverty, percent of female-headed households, male unemployment rate, and public assistance usage).

The study found that shopping in areas with a lower socioeconomic status designation relative to one's own neighborhood correlated with higher BMI (data not reported). Living in a very low socioeconomic status area resulted in a 1.5-unit increase in BMI (*P*<.001), and living in a low socioeconomic status area resulted in a 1.2-unit increase in BMI (*P*<.01) compared with living in a very high socioeconomic status area.[3] EBP

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**REFERENCES**

1. Hutchinson PL, Nicoholas Bodor J, Swalm CM, Rice JC, Rose D. Neighbourhood food environments and obesity in southeast Louisiana. *Health Place*. 2012; 18(4):8548–8860. **[STEP 3]**
2. Jilcott SB, Keyserling T, Crawford T, McGuirt JT, Ammerman AS. Examining associations among obesity and per capita farmers' markets, grocery stores/supermarkets, and supercenters in US counties. *J Am Diet Assoc*. 2011; 111(4):567–572. **[STEP 3]**
3. Inagami S, Cohen DA, Finch BK, Asch SM. You are where you shop: grocery store locations, weight, and neighborhoods. *Am J Prev Med*. 2006; 31(1):10–17. **[STEP 3]**

## Azithromycin for unscheduled cesarean delivery

Tita AT, Szychowski JM, Boggess K, Saade G, Longo S, Clark E, et al. Adjunctive azithromycin prophylaxis for cesarean delivery. *N Engl J Med*. 2016; 375(13):1231–1241..

This RCT included 14 centers in the United States and evaluated a single dose of azithromycin to prevent infection in 2,013 pregnant women undergoing nonelective cesarean delivery after the onset of labor or rupture of membranes. Of note, women with scheduled cesarean delivery and women with chorioamnionitis were excluded from this study.

Women had singleton gestations at >24 weeks' gestational age and were randomly assigned to standard antibiotic prophylaxis (usually cefazolin alone) or standard antibiotic prophylaxis plus a single intravenous (IV) dose of azithromycin 500 mg. The primary outcome was a composite of endometritis, wound infection, or other infection occurring within 6 weeks of surgery.

The primary outcome occurred less in women who received azithromycin plus standard prophylaxis than women receiving standard antibiotic prophylaxis alone (6.1% vs 12%; relative risk [RR] 0.51; 95% CI, 0.38–0.68). Significant differences also occurred in rates of endometritis (3.8% vs 6.1%; RR 0.62; 95% CI, 0.42–0.92), wound infection (2.4% vs 6.6%; RR 0.35; 95% CI, 0.22–0.56), and serious maternal adverse events (1.5% vs 2.9%; RR 0.5; 95% CI, 0.27–0.94). No difference was noted in any secondary neonatal outcomes including death and serious complications (14.3% vs 13.6%; RR 1.05; 95% CI, 0.85–1.31).

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|---|---|---|---|
| Relevant | Yes | Medical care setting | Yes |
| Valid | Yes | Implementable | Yes |
| Change in practice | Yes | Clinically meaningful | Yes |

**Bottom line:** A single IV dose of azithromycin 500 mg added to standard antibiotic prophylaxis reduces the risk of postoperative infection when given at the time of nonelective cesarean delivery during labor or after rupture of membranes.

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## Hypertension treatment goals; is it more than just a number?

Navar AM, Pencina MJ, Peterson ED. Assessing cardiovascular risk to guide hypertension diagnosis and treatment. *JAMA Cardiol*. 2016; 1(8):864–871.

This cross-sectional analysis estimated the number and characteristics of adults with systolic blood pressure (SBP) >120 mmHg in the United States. The study also used the data to determine how many patients would have met inclusion criteria for the recent SPRINT and HOPE-3 clinical trials. The SPRINT trial showed some benefit of lowering SBP to 120 mmHg while other trials like HOPE-3 did not. The authors examined data on nonpregnant adults 20–79 years old who participated in the 2007–2012 National Health and Nutrition Examination Survey (NHANES) and for whom complete cardiovascular disease (CVD) risk data were available (n=14,142).

Extrapolating to the entire US population, approximately 53.3 million untreated and 19.8 million treated adults have a SBP of 120–139 mmHg. Very few would have been eligible for SPRINT (7.7%) and HOPE-3 (3.7%). Even among patients with prior CVD or a CVD risk >15%, relatively few would have been eligible for SPRINT (25.7%) and HOPE-3 (8.3%).

The SPRINT and HOPE-3 trials may not be generalizable to the entire US population. The authors recommended using a management strategy based on CVD risk in addition to BP measurement when treating hypertension.

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

**Bottom line:** Interestingly, 2 recent hypertension treatment studies may not be generalizable. However, this analysis was not a clinical trial, had no patient outcomes, and therefore cannot be practice changing. Conflicting evidence remains regarding the exact treatment goals for BP in the general population and for individuals with specific CVD risk factors. EBP

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the Air Force at large, or the Department of Defense.

# Do you need to stop metformin in a hospitalized patient with diabetes?

### *CASE*

*A 54-year-old woman with type 2 diabetes mellitus, chronic kidney disease, and chronic obstructive pulmonary disorder (COPD) is admitted for a COPD exacerbation and a new 2L oxygen requirement. The patient weighs 90 kg; her vital signs, except for a new oxygen requirement, are normal. She is started on appropriate COPD exacerbation treatment, and during medication reconciliation, the clinician notices she takes metformin 1,000 mg BID for her well-controlled diabetes. Her serum creatinine is 1.5 mg/dL today, the same as 1 month before. Should she have her metformin discontinued while in the hospital?*

## Bottom line

Patients who were taking metformin appropriately prior to hospitalization can safely continue metformin during their hospitalization if they do not have medical risk factors for developing lactic acidosis. If patients receive iodinated contrast, they can safely continue metformin if they have an estimated glomerular filtration rate (eGFR) ≥45–60 mL/min.

## Review of the evidence

A 2016 case-controlled trial evaluated the development of biological lactic acidosis from January 2008 to December 2011 in 906 patients with type 2 diabetes admitted to the hospital.[1] Overall, 302 patients with type 2 diabetes in whom lactic acidosis developed were matched with 604 similar patients without lactic acidosis. Condition-specific logistical regression was used to determine the odds of developing lactic acidosis (defined as arterial pH <7.35 and lactate level >5 mmol/L).

Compared with patients in whom lactic acidosis did not develop, patients who took metformin and had acute kidney injury had an increased risk of lactic acidosis (odds ratio [OR] 1.8; 95% CI, 1.1–2.9); the risk was not increased in patients without kidney injury (OR 0.86; 95% CI, 0.48–1.6).

A 2010 systematic review of 347 trials examined the risk of lactic acidosis from metformin in patients with type 2 diabetes mellitus taking metformin regardless of the setting.[2] Prospective and observational cohort studies were examined when metformin was used either alone or in combination with other diabetes medications. The review included 70,490 patient-years of metformin use compared with 55,451 patient-years of nonmetformin use.

Lactic acidosis occurred at a similar rate in the metformin group as in the nonmetformin group (4.4 vs 5.4 per 100,000 patient-years; no *P* value provided). The review authors concluded that metformin was not associated with an increased risk of lactic acidosis.[2]

The 2012 Canadian Association of Radiologist consensus guideline on preventing contrast-induced nephropathy stated patients with eGFR of ≥60 mL/min had an extremely low risk of contrast-induced nephropathy and changes to metformin use were not needed.[3] The 2011 European Society of Urogenital Radiologist evidence-based guidelines stated that patients with eGFR >45 mL/min could continue taking metformin when receiving intravenous iodinated contrast.[4]

The FDA package insert update for metformin in 2016 stated that lactic acidosis was a rare adverse event and risk factors for its development are renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure. The FDA recommended metformin be stopped before an iodinated contrast procedure in patients with an eGFR of 30 to 60 mL/min.[5]

### *CASE WRAP-UP*

*Because the patient's eGFR was 60 mL/min, she was continued on metformin. She had no complications, did not require any additional imaging studies, and was discharged in 48 hours with appropriate COPD treatment and continued on her home medications.* EBP

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**REFERENCES**

1. Lepelley M, Giai J, Yahiaoui N, Chanoine S, Villier C. Lactic acidosis in diabetic population: is metformin implicated? Results of a matched case-control study performed on the type 2 diabetes population of Grenoble Hospital University. *J Diabetes Res*. 2016; 2016:3545914. **[STEP 4]**
2. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2010; (4):CD002967. **[STEP 3]**
3. Owen RJ, Hiremath S, Myers A, Fraser-Hill M, Barrett BJ. Canadian Association of Radiologists consensus guidelines for the prevention of contrast-induced nephropathy: update 2012. *Can Assoc Radiol J*. 2014; 65(2):96–105. **[STEP 5]**
4. Stacul F, van der Molen AJ, Reimer P, Webb JA, Thomsen HS, Morcos SK, et al. Contrast induced nephropathy: updated ESUR contrast media safety committee guidelines. *Eur Radiol*. 2011; 21(12):2527–2541. **[STEP 5]**
5. US Food and Drug Administration. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. https://www.fda.gov/Drugs/DrugSafety/ucm493244.htm. Last updated April 5, 2017. Accessed September 21, 2017. **[STEP 5]**

## What is the best noninvasive test of cure to confirm eradication of *H pylori* infection?

### EVIDENCE-BASED ANSWER

The urea breath test (UBT) and monoclonal stool antigen test (SAT) have similar sensitivities (95% and 91%) and specificities (100% and 97%) and similarly low negative likelihood ratios (LR– 0.05 for UBT and 0.09 for SAT) for confirming eradication of *Helicobacter pylori*. The sensitivity of UBT is decreased by use of proton-pump inhibitors, and so should not be used in patients taking those medications. *H pylori* serology remains positive long after eradication and is not useful to confirm eradication (SOR: **B**, diagnostic cohort studies, cohort study, and longitudinal study).

A diagnostic cohort study from 1999 studied the correlation of upper gastrointestinal endoscopy (EGD) with biopsy for the diagnosis of *H pylori* infection versus carbon-13 UBT, administered with citric acid solution in more than 500 European patients with dyspepsia symptoms.[1] Prevalence of infection of *H pylori* in this population was not specified. Overall, 60 patients of this cohort with positive culture or positive histology and UBT for *H pylori*, were then reexamined for eradication 4 weeks after treatment with both tests. UBT had a posttreatment sensitivity of 95%, a specificity of 100%, and a low LR– (0.05).

A 2006 diagnostic cohort study of 97 European patients 8 weeks after eradication treatment of *H pylori* evaluated 4 different types of SATs (2 rapid monoclonal immunochromatography tests, 1 monoclonal enzyme immunoassay [EIA] test, and 1 polyclonal EIA test) compared with UBT or gastric biopsy.[2] The best SAT (monoclonal ImmunoCard STAT) had a sensitivity of 91% and a specificity of 97% (LR– 0.09). The prevalence of *H pylori* infection in this population was not specified.

A prospective cohort study in 40 patients with *H pylori* diagnosed by gastric biopsy evaluated the effect of 2 weeks of lansoprazole (15 mg tid, n=20) or ranitidine (150 mg bid, n=20) on the accuracy of the UBT (100 mg of carbon-13 urea dissolved in 50 mL glucose polymer).[3] After 2 weeks of lansoprazole, a follow-up UBT was negative in 8 patients (40% false negative) and after a further 2 weeks it was negative in 2 patients (10% false negative). The UBT showed no false-negative results in patients after 2 weeks of ranitidine.

A longitudinal study from 1998 followed 29 patients with biopsy-proven *H pylori* and positive ELISA IgG *H pylori* antibodies after successful eradication with antibiotic treatment, confirmed by negative UBT.[4] Even though UBT results remained negative and patients had no symptoms, 72% of patients had a seropositive ELISA test result as long as 3.5 years after treatment.

Both the 2007 American College of Gastroenterology and the 2012 Maastricht IV consensus reports stated that confirmation of eradication is not necessary in low-risk patients.[5,6] In high-risk patients—patients with severe gastritis, *H pylori*-induced ulcer, persistent symptoms, a history of gastric cancer, risk factors for gastric cancer, or with MALT lymphoma—confirmation of eradication should be obtained by either UBT or SAT, not serology.

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1. Leodolter A, Dominguez-Muñoz JE, von Armin U, Kahl S, Peitz U, Malfertheiner P. Validity of a modified $^{13}$C-urea breath test for pre- and posttreatment diagnosis of *Helicobacter pylori* infection in the routine clinical setting. *Am J Gastroenterol*. 1999; 94(8):2100–2104. **[STEP 2]**
2. Quesada M, Calvet X, Dosal A, Calvet V, Sanfeliu I, Ribera L, et al. Evaluation of four different fecal tests for determination of cure after *Helicobacter pylori* treatment. *J Clin Gastroenterol*. 2006; 40(9):790–794. **[STEP 2]**
3. Bravo LE, Realpe JL, Campo C, Mera R, Correa P. Effects of acid suppression and bismuth medications on the performance of diagnostic tests for *Helicobacter pylori* infection. *Am J Gastroenterol*. 1999; 94(9):2380–2383. **[STEP 3]**
4. Cutler AF, Prasad VM, Santogade P. 4 year trends in Helicobacter pylori IgG serology following successful eradication. *Am J Med*. 1998; 105(1):18–20. **[STEP 3]**
5. Chey WD, Wong BC; for the Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007; 102(8):1808–1825. **[STEP 5]**
6. Malfertheiner P, Megraud F, O'Morain C, Atherton J, Axon AT, Bazzoli F, et al. Management of *Helicobacter pylori* infection—the Maastricht IV/ Florence Consensus Report. *Gut*. 2012; 61(5):646–664. **[STEP 5]**

### *EVIDENCE-BASED PRACTICE* LEARNING OBJECTIVES

**1** To become knowledgeable about evidence-based solutions to commonly encountered clinical problems.

**2** To understand how ground-breaking research is changing the practice of family medicine.

**3** To become conversant with balanced appraisals of drugs that are marketed to physicians and consumers.

## Does the addition of corticosteroids to standard treatment affect neurologic sequelae in patients with bacterial meningitis?

### EVIDENCE-BASED ANSWER

The addition of corticosteroids to standard treatment for bacterial meningitis does not reduce mortality except in cases of *Streptococcus pneumoniae* meningitis. The addition of corticosteroids is associated with decreased hearing loss and short-term neurological sequelae at the expense of a small increased risk of recurrent fever. No significant benefit is gained from using corticosteroids for bacterial meningitis in low-income countries (SOR: **A**, meta-analysis of RCTs). Dexamethasone should be given when *S pneumoniae* meningitis is suspected in adults, or when *Haemophilus influenzae* meningitis is suspected in infants and children (SOR: **C**, expert opinion)

A 2015 systematic review with meta-analysis of 25 RCTs examined the addition of corticosteroids to standard treatment for bacterial meningitis in 4,121 patients (2,511 children, 1,517 adults, and 93 mixed population).[1] Most studies evaluated the effect of corticosteroids on mortality, hearing loss, or neurologic sequelae. Hearing loss was defined as severe if it was bilateral and either more than 60 decibels or requiring hearing aids. Neurological sequelae included focal neurologic deficits, new epilepsy, severe ataxia, or severe memory or concentration disturbance. Neurological sequelae were further divided into short-term (0–6 weeks) and long-term (6–52 weeks).

No significant decrease in mortality was found when corticosteroids were added to treatment for bacterial meningitis (risk ratio [RR] 0.90; 95% CI, 0.80–1.01). However, a subgroup analysis showed that the mortality rate decreased significantly in patients with *S pneumoniae* meningitis (17 studies, n=1,132; RR 0.84; 95% CI, 0.72–0.98), but not with meningitis due to *Neisseria meningitides* or *H influenzae*.[1]

Corticosteroid use resulted in less severe hearing loss (17 studies, n=2,437; RR 0.67; 95% CI, 0.51–0.88), any hearing loss (20 studies, n=2,785; RR 0.74; 95% CI, 0.63–0.87), and short-term neurological sequelae (13 studies, n=1,756; RR 0.83; 95% CI, 0.69–1.00). Corticosteroid use did not improve the risk of long-term neurological sequelae (13 studies, n=1,706; RR 0.90; 95% CI, 0.74–1.10). When data were pooled from the 4 highest quality studies, the beneficial effect of corticosteroids on severe hearing loss was not significant. In children, corticosteroids reduced the rate of severe hearing loss in patients with *H influenzae* meningitis (10 studies, n=756; RR 0.34; 95% CI, 0.20–0.59), but not with other causative organisms.[1]

The authors evaluated the incidence of adverse events including gastrointestinal bleeding, reactive arthritis, pericarditis, herpes zoster, herpes simplex, fungal infection, recurrent fever (temperature >38°C after 1 afebrile day during the primary hospitalization), and persistent fever (fever >5 days after initiation of appropriate antibiotic therapy). Only recurrent fever was significantly greater in groups receiving corticosteroids (12 studies, n=1,723; RR 1.27; 95% CI, 1.09–1.47).[1]

The review included 16 RCTs from high-income and 9 from low-income countries. In high-income countries, corticosteroid use resulted in lower rates of severe hearing loss (12 studies, n=1,501; RR 0.51; 95% CI, 0.35–0.73), any hearing loss (13 studies, n=1,754; RR 0.58; 95% CI, 0.45–0.73), and short-term neurological sequelae (9 studies, n=1,079; RR 0.64; 95% CI, 0.48–0.85). Studies from low-income countries, however, did not show a measureable benefit from corticosteroids.[1]

Clinical practice guidelines from the Infectious Diseases Society of America (IDSA) support the use of dexamethasone when S pneumoniae meningitis is suspected in adults.[2] Dexamethasone (0.15 mg/kg every 6 hours for 2–4 days) was recommended immediately after cerebral spinal fluid (CSF) is collected, before or at the time of the first dose of antibiotics. Similarly, in infants and children with *H influenzae* meningitis, the IDSA advocated using dexamethasone 0.15 mg/kg every 6 hours for 2 to 4 days. In both cases, the practice guidelines advised that the corticosteroids be continued only if CSF and blood cultures confirm the causative organism.

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1. Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2015; (9):CD004405. **[STEP 1]**
2. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004; 39(9):1267–1284. **[STEP 5]**

## What is the optimal education structure for improving diabetes control and minimizing distress in patients with type 2 diabetes?

### EVIDENCE-BASED ANSWER

Group-based and individual-based diabetes education reduces glycosylated hemoglobin (HbA1C) slightly more than routine provider visits, with greater effect seen in patients with higher baseline HbA1C (SOR: **C**, meta-analyses of RCTs and single cohort study with disease-oriented evidence). The differences in HbA1C between individual and group education at 6 months are inconsistent, but no difference is apparent after 12 months (SOR: **C**, inconsistent meta-analysis of RCTs and single RCT with disease-oriented outcomes). Less time-intensive individual sessions monthly are slightly better than more time-intensive group sessions weekly at reducing HbA1C and diabetes-related distress (SOR: **B**, RCT).

A 2012 meta-analysis of 21 RCTs (N=2,833, mean age 60 years, mean HbA1C 8.2%) compared group-based diabetes self-management education (DSME) with controls of routine treatment with scheduled provider visits presumably with some education (16 trials), waiting list controls (4 trials), or no intervention (1 trial).[1] Group DSME ranged from a single 1-hour session to 52 hours spread over 12 months.

Reduction in HbA1C was larger with group DSME at 6 months (13 trials, n=1,827; mean difference [MD] –0.44%; 95% CI, –0.69 to –0.19), 12 months (11 trials, n=1,503; MD –0.46%; 95% CI, –0.74 to –0.18), and 2 years (3 trials, n=397; MD –0.87%; 95% CI, –1.3 to –0.49) compared with control.[1]

A 2009 meta-analysis of RCTs and controlled clinical trials included 6 studies (n=998) comparing individual DSME with usual care, and 3 studies (n=361) comparing individual DSME with group DSME and their effect on HbA1C in patients with new and established diabetes.[2] Individual DSME consisted of face-to-face sessions varying in duration and number addressing self-management topics over 6 to 12 months. Usual care consisted of regular follow-up from a healthcare provider, presumably with some education by that provider. Group DSME structure was unspecified. Methodology among the studies differed considerably.

For patients with a baseline HbA1C of more than 8%, individual DSME reduced HbA1C more than usual care (3 trials, n=424; weighted MD 0.3%; 95% CI, 0.1–0.5). A comparison between group and individual DSME yielded mixed results favoring group DSME over individual DSME at 6 to 9 months (2 trials, n=148; weighted MD 0.8%; 95% CI, 0.3–1.3), but not at 12 to 18 months (2 trials, n=112; weighted MD 0.03%; 95% CI, –0.02 to 0.1).[2]

A 2011 multisite RCT compared individual DSME (n=246), group DSME (n=243), and usual care (n=134) in individuals with established diabetes, with follow-up at 6.8 months.[3]

Patients in the individual DSME arm had three 1-hour sessions monthly, the group DSME arm had four 2-hour sessions weekly, and the usual-care group received just regular provider visits. Both DSME groups followed curricula consistent with the American Association of Diabetes Educators Seven Self-Care Behaviors to improve knowledge and skills in diet, monitoring, taking medications, problem solving, risk reduction, healthy coping, and being active. The individual DSME arm was led by certified diabetes educators and the group DSME arm was led mostly by certified diabetes educators who had received training on facilitating group sessions.[3]

HbA1C decreased more in the individual DSME arm (–0.51%) than the group DSME arm (–0.27%; *P*=.01) or the usual-care arm (–0.24%; *P*=.01). Diabetic distress was evaluated using the Problem Areas in Diabetes scale (a 20-item measure of diabetes-specific emotional distress, ranging from 0=low to 100=high). Individual DSME reduced diabetic distress 3.6 points more than group DSME (*P*=.02).[3]

A 2014 retrospective cohort study (N=1604) compared patients (n=802, mean age 57 years, mean HbA1C 7.6%) receiving 5 to 7 hours of group DSME led by a diabetes nurse and dietitian over 1 or 2 days within 6 months of diagnosis with patients (n=802) who did not attend group DSME but received care and presumably education from their regular provider.[4] Topics included management, diet, exercise, stress, self-monitoring, and medication.

At the 6- to 18-month follow-up, patients participating in group DSME lowered HbA1C 0.30% more than patients in the control group (95% CI, 0.20–0.39). Subset analysis showed

greater improvement with a higher starting HbA1C (0.56% for baseline HbA1C 11% vs 0.25% for baseline HbA1C 7%; *P* values not reported).[4]

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1. Steinsbekk A, Rygg LØ, Lisulo M, Rise MB, Fretheim A. Group based diabetes self-management education compared to routine treatment for people with type 2 diabetes mellitus. A systematic review with meta-analysis. *BMC Health Serv Res*. 2012; 12:213. **[STEP 1]**
2. Duke S-AS, Colagiuri S, Colagiuri R. Individual patient education for people with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2009; (1):CD005268. **[STEP 1]**
3. Sperl-Hillen J, Beaton S, Fernandes O, Von Worley A, Vazquez-Benitez G, Parker E, et al. Comparative effectiveness of patient education methods for type 2 diabetes: a randomized controlled trial. *Arch Intern Med*. 2011; 171(22):2001–2010. **[STEP 2]**
4. Weaver RG, Hemmelgarn BR, Rabi DM, Sargious PM, Edwards AL, Manns BJ, et al. Association between participation in a brief diabetes education programme and glycaemic control in adults with newly diagnosed diabetes. *Diabet Med*. 2014; 31(12):1610–1614. **[STEP 3]**

## What is the clinical significance of a small pericardial effusion incidentally discovered on CT or echocardiogram?

### EVIDENCE-BASED ANSWER

The presence of a small asymptomatic pericardial effusion is associated with a 20% increase in mortality at 1 year and is more common in patients with heart failure with reduced ejection fraction, diabetes mellitus, renal disease, and malignancy. Most (94%) effusions resolve or remain unchanged by 1-year follow-up evaluation (SOR: **B**, retrospective cohort study). Follow-up evaluation of a pericardial effusion should be based primarily on the size of the effusion, symptoms, and other clinical features such as known associated disease or inflammatory markers. Idiopathic effusions of less than 1 cm generally do not need follow-up (SOR: **C**, expert opinion).

A 2011 retrospective cohort study evaluated the prevalence, associations, and outcomes of small pericardial effusion noted incidentally on echocardiography.[1] Patients were excluded for suspected pericardial disease; having cardiac surgery within the prior 60 days; having a moderate or greater pericardial effusion (>1 cm circumferential average); or no follow-up after echocardiography. After exclusion, 9,350 patients were included in the study and 534 (5.7%) were identified as having a small pericardial effusion (<1 cm circumferential average).

Compared with patients with no pericardial effusion, patients with an effusion were slightly older (68 vs 67 years) and more likely to have a history of heart failure (9% vs 4%; *P*<.0001), diabetes mellitus (13% vs 9%; *P*=.0008), renal disease (4% vs 2%; *P*=.01), malignancy (14% vs 10%; *P*=.01), a lower left ventricular ejection fraction (mean 52% vs 55%; *P*<.0001), left atrial enlargement (44% vs 36%; *P*=.003), and moderate or greater mitral regurgitation (14% vs 10%; *P*=.007) or tricuspid regurgitation (11% vs 7%; *P*=.006).[1]

The mortality rate was higher at 1 year for patients with a small pericardial effusion than patients with no effusion (26% vs 11%; *P*<.0001). After adjustment for patient demographics, medical history, location (inpatient vs outpatient), and other echocardiographic findings, the presence of a small effusion was associated with increased mortality compared with no effusion (hazard ratio [HR] 1.2; 95% CI, 1.1–1.3). Of patients with an effusion, 40% (n=211) underwent follow-up echocardiography a mean of 547 days later. Among these patients, 64% had complete resolution of the effusion; 30% showed no change; and 5.7% had an increase in size of the effusion.[1]

Evidence-based clinical practice guidelines by the European Society of Cardiology (ESC) in 2015 recommended that follow-up of a pericardial effusion be based on symptoms, the echocardiographic size of the effusion, and other clinical features such as associated diseases or inflammatory markers (ie, C-reactive protein).[2] The ESC guidelines stated that a small (<10 mm) asymptomatic idiopathic effusion is generally associated with a low risk of complications (ie, cardiac tamponade) and does not require follow-up (consensus opinion). The ESC recommended that moderate effusions (10–20 mm) be reassessed by echocardiography every 6 months and that large effusions (>20 mm) be followed up every 3 to 6 months (consensus opinion).

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1. Mitiku TY, Heidenreich PA. A small pericardial effusion is a marker of increased mortality. *Am Heart J*. 2011; 161(1):152–157. **[STEP 2]**
2. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2015; 36(42):2921–2964. **[STEP 5]**

## In patients presenting with pneumonia, is a negative MRSA PCR nasal swab useful for ruling out MRSA as the causative agent?

### EVIDENCE-BASED ANSWER

The answer is unclear. In adults admitted for pneumonia, the methicillin-resistant *Staphylococcus aureus* (MRSA) nasal swab polymerase chain reaction (PCR) swab has negative likelihood ratios that vary from 0.97 to 0.07 across studies (SOR: **C**, inconsistent prospective and retrospective cohort studies).

A 2010 prospective cohort study of 749 patients admitted to an intensive care unit (ICU) examined the use of MRSA nasal PCR screening for predicting presence of MRSA infection that would require antibiotics.[1] Nasal swabs were obtained at admission and weekly thereafter; 183 patients (24.2%) had positive MRSA nasal swab PCR results: 164 tested positive at the time of ICU admission and 19 converted during their ICU stay.

Of the 749 patients, 178 (23.8%) acquired a MRSA infection diagnosed by culture during their ICU stay: 100 had MRSA lower respiratory tract infections (LRTIs), 58 had bloodstream infections, and 20 had both. The percent of patients with LRTIs that had a positive MRSA nasal swab PCR was not reported, but a negative MRSA nasal swab PCR on admission had a negative likelihood ratio (LR–) for MRSA LRTI of 0.97.[1]

In a 2014 retrospective cohort study (N=435), a laboratory database was reviewed for patients who had both a MRSA nasal swab PCR and either a blood or a respiratory culture result, in order to evaluate the performance of nasal swab PCR in predicting culture-confirmed MRSA pneumonia.[2] Charts were reviewed and included if patients met criteria for pneumonia and excluded if another diagnosis was more likely, or if the swab had been obtained either more than 1 month (if presenting from an outpatient setting) or more than 7 days (if admitted) before obtaining the culture.

Of the 25 patients with a positive MRSA culture, 22 had a positive MRSA nasal swab PCR; in the 410 patients with negative cultures, 370 had a negative nasal swab. A negative MRSA nasal swab PCR had a LR– for MRSA pneumonia of 0.13.[2]

A 2015 retrospective cohort study (N=297) evaluated adult patients, admitted to either the medical ward or ICU, who had both MRSA nasal swab PCRs and respiratory cultures (the latter obtained within 48 hours before or after collection of the swab).[3]

Of the 14 patients with MRSA-positive cultures, 12 had positive MRSA nasal swab PCRs; of the 283 patients with negative cultures, 263 had negative MRSA nasal swab PCRs. The LR– for a negative MRSA nasal swab PCR for MRSA respiratory cultures was 0.15.[3]

A 2015 retrospective cohort (N=72) study of patients admitted to an urban teaching hospital evaluated the use of MRSA nasal swab PCR in identifying MRSA respiratory infections in order to guide deescalation of antibiotic regimens.[4] Both nasal swab and culture had to be obtained within 48 hours of admission. All patients had a positive *S aureus* lower respiratory culture obtained via sputum, tracheal aspirate, bronchoalveolar lavage, or bronchial wash or brush. Forty-nine patients were admitted to the ICU and 23 to the medical ward.

A total of 30 were identified with MRSA-positive cultures, of whom 28 also had a positive MRSA nasal swab PCR. Overall, 42 patients had cultures positive for methicillin-sensitive *S aureus* (ie, negative for MRSA) and of those, 40 had a negative MRSA nasal swab PCR. The LR– with a negative MRSA nasal swab PCR for MRSA respiratory cultures was 0.07.[4]

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1. Sarikonda KV, Micek ST, Doherty JA, Reichley RM, Warren D, Kollef MH. Methicillin-resistant *Staphylococcus aureus* nasal colonization is a poor predictor of intensive care unit-acquired methicillin-resistant *Staphylococcus aureus* infections requiring antibiotic treatment. *Crit Care Med*. 2010; 38(10):1991–1995. **[STEP 2]**
2. Dangerfield B, Chung A, Webb B, Seville MT. Predictive value of methicillin-resistant *Staphylococcus aureus* nasal swab PCR assay for MRSA pneumonia. *Antimicrob Agents Chemother*. 2014; 58(2): 859–864. **[STEP 3]**
3. Hiett J, Patel RK, Tate V, Smulian G, Kelly A. Using active methicillin-resistant *Staphylococcus aureus* surveillance nasal swabs to predict clinical respiratory culture results. *Am J Health Syst Pharm*. 2015; 72(11 suppl 1):S20–S24. **[STEP 3]**
4. Johnson JA, Wright ME, Sheperd LA, Musher DM, Dang BN. Nasal methicillin-resistant *Staphylococcus aureus* polymerase chain reaction: a potential use in guiding antibiotic therapy for pneumonia. *Perm J*. 2015; 19(1):34–36. **[STEP 3]**

## Is vision testing effective in preventing driving fatalities in older adults?

### EVIDENCE-BASED ANSWER

US state driver's license policies that include vision testing for older adults are associated with a 2% to 8% lower risk of fatal automobile accidents (SOR: **C**, secondary analyses of a cross-sectional administrative database).

A cross-sectional analysis of data from the US Fatal Accident Reporting System (FARS) examined annual motor vehicle fatality rates for drivers 80 years and older in Florida, 3 years before and 3 years after a new relicensing law passed in 2004.[1] The law included a new in-person vision acuity test or a letter from a doctor stating the licensee passed a vision screening test within the past year.

In the 3 years after implementation of the law, vehicle fatality rates (per 100,000 population per year) decreased among drivers 80 years old and older, compared with the 3 years prior (12.3 vs 14.9; risk ratio [RR] 0.83; 95% CI, 0.72–0.98, adjusted for age, sex, and race). Conversely, fatality rates for all Florida drivers showed no significant change. Furthermore, in the neighboring states of Georgia and Alabama (which did not require the visual acuity test), the motor vehicle fatality rates for drivers 80 years old and older were stable during this 6-year time frame.[1]

An earlier analysis of FARS data examined the relationship between license renewal policies for older drivers in the 48 contiguous states and 40,590 fatal crashes (1990–2000) involving drivers 65 and older.[2] Policies such as in-person renewal, vision tests, road tests, and the interval between required license renewals were analyzed. Researchers studied total vehicle fatalities in 3 age groups: 65 to 74, 75 to 84, and 85 and older. They also compared total fatalities that happened at any hour with fatalities occurring during the daytime (7 AM to 7 PM). Outcomes were adjusted for age, unemployment rate, income, speed limits, and state seatbelt, license suspension, and blood alcohol level laws.

Vision testing for older drivers in 40 states with this requirement (vs 8 without) was associated with a reduction in all-hour fatalities for drivers 65 to 74 years old (RR 0.92; 95% CI, 0.85–0.99), but not for the 75- to 84-year-old group nor >85 cohorts. Mandatory vision testing made no difference in the number of daytime fatal accidents for any of the cohorts.[2]

A similar study of FARS data assessed the association between driver's license renewal policies and 16,840 fatal crashes (1985–1989) involving drivers 70 years and older in 50 US states.[3] Policies involving road, knowledge, vision tests, and the interval between required license renewals were examined. The researchers adjusted for multiple variables including age, miles traveled per licensed driver, average highway driving speed, speed variation, proportion of trucks among registered vehicles, urban and rural driving mix, per-capita income, hospitals per capita, and year.

States (n=40) with visual acuity tests were associated with a lower fatal crash risk than states without (RR 0.93; 95% CI, 0.89–0.97).[3]

A limitation of all 3 studies was the inability to infer causation between vision testing and fatal crashes because of the cross-sectional nature of the studies. Although all studies adjusted for various confounding variables, other unmeasured variables in the states could possibly have contributed to the associations reported. All studies used FARS data, which excluded nonfatal crashes, possibly misclassified drivers not licensed in the state in which they crashed, and did not indicate which driver was at fault.

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1. McGwin G, Sarrels SA, Griffin R, Owsley C, Rue LW. The impact of a vision screening law on older driver fatality rates. *Arch Ophthalmol*. 2008; 126(11):1544–1547. **[STEP 3]**
2. Grabowski DC, Campbell CM, Morrisey MA. Elderly licensure laws and motor vehicle fatalities. *JAMA*. 2004; 291(23):2840–2846. **[STEP 3]**
3. Levy DT, Vernick JS, Howard KA. Relationship between driver's license renewal policies and fatal crashes involving drivers 70 years or older. *JAMA*. 1995; 274(13):1026–1030. **[STEP 3]**

## Does use of preexposure prophylaxis for HIV increase the rate of other sexually transmitted infections in men who have sex with men?

### EVIDENCE-BASED ANSWER

No, the use of preexposure prophylaxis (PrEP) in men who have sex with men (MSM) does not lead to an increase in the incidence of bacterial sexually transmitted infections (STIs) (SOR: **A**, 2 RCTs and a single prospective cohort study).

An open-label, randomized PrEP efficacy trial in MSM also evaluated the rates of bacterial STI (chlamydia, gonorrhea, and syphilis).[1] The 544 participants enrolled between 2012 and 2014 from 13 sexual health clinics in England were 18 years old or older, HIV negative, and reported unprotected anal intercourse in the past 90 days; 273 of these men were placed on PrEP.

After 1 year, 57% of PrEP recipients versus 50% of deferred patients tested positive for bacterial STIs. When adjusted to account for the increased test frequency in PrEP participants, the difference in positive bacterial STI tests between groups was insignificant (odds ratio [OR] 1.1; 90% CI, 0.78–1.5). PrEP participants were more likely to report unprotected receptive anal sex with 10 or more partners (21% vs 12%; *P*=.03), but were no more likely to be diagnosed with rectal gonorrhea or chlamydia, a marker for unprotected receptive anal intercourse (36% vs 32%; adjusted OR 1.0; 90% CI, 0.72–1.4). This study was limited by a relatively small study population, potential observer effect due to open-label design, and limited longitudinal data collected regarding sexual risk behaviors.[1]

A 2015 double-blind randomized trial of on-demand PrEP followed 400 MSM patients from 2012 to 2014 who were 18 years old or older reporting unprotected receptive anal intercourse with 2 or more partners during the past 6 months.[2] Participants were from 6 sites across France and Canada and were followed for a median of 9.3 months (interquartile range, 4.9–21 months) during which time new HIV infections (primary measure) were tracked, along with medication side effects, STI rates, and sexual behavior patterns.

Although the control group had slightly fewer sexual partners than the PrEP group (7.5 vs 8 in the previous 2 months), no significant differences were noted in rates of new STIs, sexual intercourse, or unprotected receptive anal intercourse. Study limitations included a relatively small sample size and potential inaccuracy of self-reporting of sexual risk behaviors.[2]

From 2012 to 2015, an open-label, multicenter cohort study followed 557 HIV-negative MSM patients 18 years old or older reporting unprotected receptive anal intercourse with multiple partners, receptive anal sex with an HIV-infected partner, or rectal STI infection in the past year.[3] Participants were placed on PrEP and followed for 48 weeks.

STI incidence rates (90 per 100 person-years) and average rates of receptive anal sex without a condom (66%) remained stable across quarterly intervals. Study limitations included underrepresentation of African American and transgender participants.[3]

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1. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet*. 2016; 387(10013):53–60. **[STEP 2]**
2. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med*. 2015; 373(23):2237–2246. **[STEP 2]**
3. Liu AY, Cohen SE, Vittinghoff E, Anderson PL, Doblecki-Lewis S, Bacon O, et al. Preexposure prophylaxis for HIV infection integrated with municipal- and community-based sexual health services. *JAMA Intern Med*. 2016; 176(1):75–84. **[STEP 3]**

## Is methotrexate effective in maintaining remission in Crohn's disease?

### EVIDENCE-BASED ANSWER

Methotrexate (MTX) may be effective for maintaining remission in patients with moderately severe Crohn's disease compared with placebo (SOR: **B**, systematic reviews of heterogeneous RCTs).

A 2013 American Gastroenterology Association Institute technical review of medical treatments for Crohn's disease pooled data from 2 RCTs evaluating the effectiveness of MTX for maintaining remission, defined as a Crohn's Disease Activity Index (CDAI) score of less than 150.[1] CDAI

is a validated research tool that quantifies multiple Crohn's disease signs and symptoms.

In 1 RCT, 76 patients with moderate to severe Crohn's disease who achieved remission with once-weekly intramuscular (IM) MTX 25 mg for 16 to 24 weeks were randomized to weekly IM MTX 15 mg or placebo with no additional therapy for 40 weeks. In the other RCT, 52 adult patients with Crohn's disease with a baseline CDAI score of less than 150 who had been treated with steroids and/or immunosuppressives for 4 months in the preceding year received oral MTX 12.5 mg or placebo for 9 months. Cotreatment with steroids or 5-aminosalycilic acid was allowed in both the MTX and placebo groups.[1]

After pooling data from these 2 trials, MTX was associated with fewer disease relapses than placebo (risk ratio [RR] 0.74; 95% CI, 0.54–1.0). The review authors calculated 168 fewer relapses per 1,000 patients over the course of treatment (95% CI, 0–297). The evidence was of low quality due to significant heterogeneity in the treatment regimens. Oral MTX is no longer considered appropriate treatment for Crohn's disease.[1]

A 2011 systematic review identified an additional RCT that assessed the effectiveness of MTX in maintaining remission of Crohn's disease compared with placebo.[2]

This study evaluated 28 corticosteroid-dependent patients given either oral MTX 15 mg once weekly or placebo for 1 year or until treatment failure, defined as a Crohn's flare or significant side effects from treatment.[3] All patients were prednisone dependent for at least 6 months and all but 1 had either a CDAI score of more than 150 using prednisone 10 mg or a CDAI score of less than 150 using prednisone 15 mg or higher. Some patients were adjusted to oral MTX 22.5 mg once a week at the discretion of the principal investigator. No statistical difference in relapses was noted between the 2 groups.

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1. Dassopoulos T, Sultan S, Falck-ytter YT, Inadomi JM, Hanauer SB. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology*. 2013; 145(6):1464–1478.e1–5. **[STEP 1]**
2. Talley NJ, Abreu MT, Achkar JP, Bernstein CN, Dubinsky MC, Hanauer SB, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. *Am J Gastroenterol*. 2011; 106(suppl 1):S2–S25. **[STEP 1]**
3. Arora S, Katkov W, Cooley J, Kemp JA, Johnston DE, Schapiro RH, et al. Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. *Hepatogastroenterology*. 1999; 46(27):1724–1729. **[STEP 2]**

## Is dialectic behavioral therapy effective in reducing symptoms or characteristics of borderline personality disorder compared with usual treatment?

### EVIDENCE-BASED ANSWER

Dialectic behavioral therapy (DBT) is effective in improving some symptoms of borderline personality disorder such as anger, suicidality, parasuicidality, anxiety, depression, self-harm, and overall mental health status (SOR: **B**, meta-analysis of low-to-moderate quality RCTs and 1 additional small RCT). DBT should be considered for reducing self-harm behavior in women (SOR: **C**, expert opinion).

A 2012 systematic review analyzed 5 RCTs (N=252) of women (mean ages 27–43 years) with borderline personality disorder (BPD), with or without comorbid substance abuse, comparing outpatient DBT with usual care.[1] Participants were diagnosed by DSM-III, DSM-III-R, or DSM-IV criteria. DBT consisted of 6 or 12 months of weekly individual and group therapy, with or without telephone access to therapists. Usual care included individual counseling, group therapy, and therapy referral. Outcomes were measured using several different scales; thus, results were reported as standardized mean differences.

DBT led to moderate improvements in mental health status/functioning as well as moderate-to-large reductions in inappropriate anger, suicidality, parasuicidality, depression, and anxiety compared with usual care (see **TABLE**). No between-group differences were noted in BPD total severity, impulsivity, interpersonal problems, dissociation, or treatment adherence. Overall, the authors concluded there was a beneficial effect of DBT on BPD, although the evidence was of low-to-moderate quality. Studies were small with single or few studies for each outcome and affected by allegiance bias (inferences made about study results are tainted by researchers' expectations and beliefs) and attention bias (unequal amounts of attention given to intervention vs control groups).[1]

A subsequent RCT examined the effectiveness of outpatient DBT for 42 patients with cluster B personality disorders.[2] Overall, 90% of participants had BPD based on the Structured Clinical Interview for DSM Axis II disorders.

**TABLE**

**Meta-analysis of dialectic behavioral therapy (DBT) versus usual care in patients with borderline personality disorder[1]**

| Outcome | No. of RCTs | No. of patients | Standardized mean difference (95% CI) |
|---|---|---|---|
| Mental health status/functioning | 2 | 74 | 0.7 (0.1 to 1.2) |
| Inappropriate anger | 2 | 46 | –0.8 (–1.4 to –0.2) |
| Suicidality | 1 | 20 | –1.3 (–2.2 to –0.3) |
| Parasuicidality | 3 | 110 | –0.5 (–0.9 to –0.2) |
| Depression | 1 | 20 | –1.1 (–2.1 to –0.2) |
| Anxiety | 1 | 20 | –1.2 (–2.2 to –0.3) |

Standard mean difference scores around 0.2 were considered to represent a small clinical effect, scores of 0.5 as moderate, and scores of ≥0.8 as large.

Patients were adults (71% women) with a mean age of 35 years; 90% were unemployed. DBT included 1 hour of individual therapy and 2.5 hours of group skills training weekly, as well as limited telephone access to therapists for 1 year. Control group participants received treatment as usual, including outpatient psychiatry, case management, psychotherapy, inpatient admission, drug and alcohol treatment, and crisis management. The primary outcome was the self-administered Clinical Outcomes in Routine Evaluation Outcome Measure (CORE-OM), consisting of 34 questions scored 0 to 4 points exploring 4 dimensions: (1) subjective well-being, (2) psychiatric and physical problems, (3) life functioning, and (4) risk of harm to self or others. Total scores range from 0 to 136, with higher scores indicating more distress.

DBT decreased total CORE-OM score from 88 to 80 over 12 months while usual care decreased scores from 82 to 75, but the difference between groups was not significant. In the dimension of harm to self or others, the DBT group had a per-question score drop over 12 months of 0.3 points, while patients in the control group had an increase of 0.1 point ($P$<.04). No differences were noted in the other 3 dimensions.[2]

This RCT was limited by lack of DBT intervention expert oversight and adherence measurement, high dropout rates (23%), small sample size, reliance on self-report measures without objective verification, lack of successful blinding of assessors, and no measurement of hours spent in usual care.[2]

The National Institute for Health and Care Excellence 2009 evidence-based guideline recommended against brief psychological interventions (of <3 months' duration) for patients with BPD, and noted that DBT should be considered for women with BPD for whom reducing recurrent self-harm is a priority.[3] Evidence was rated as very low to moderate. EBP

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1. Stoffers JM, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Psychological therapies for people with borderline personality disorder. *Cochrane Database Syst Rev*. 2012; (8):CD005652. **[STEP 1]**
2. Feigenbaum JD, Fonagy P, Pilling S, Jones A, Wildgoose A, Bebbington PE. A real-world study of the effectiveness of DBT in the UK National Health Service. *Br J Clin Psychol*. 2012; 51(2):121–141. **[STEP 2]**
3. National Institute for Health and Care Excellence. Borderline personality disorder: recognition and management. Clinical practice guideline no. 78. http://nice.org.uk/guidance/cg78. Published January 2009. Accessed November 9, 2017. [STEP 5]

# Is butterbur an effective treatment for allergic rhinitis?

## Bottom line

An herbal medicine derived from extracts of the butterbur plant (*Petasites hybridus*) is more effective than placebo and similar in effectiveness to second-generation antihistamines for relieving symptoms of allergic rhinitis over 1 to 2 weeks, with about a third of patients responding (SOR: **B**, systematic review of short-term RCTs and single crossover study). However, unpurified butterbur has hepatotoxic properties and long-term safety and efficacy data are lacking.

## Evidence summary

A 2007 systematic review assessed the efficacy of herbal medicines for treating allergic rhinitis in adults.[1] Six double-blind RCTs (4 with adults and 2 without age specification; N=720) compared butterbur (most commonly 100 mg daily) with placebo or a second-generation antihistamine (fexofenadine 180 mg/d or cetirizine 10 mg/d). Detailed numerical outcome data were not reported, and meta-analysis was not performed due to heterogeneity in study design.

Four of the 5 studies that compared butterbur extract with placebo found a statistically significant benefit in the butterbur group in subjective assessment of symptoms (Total Nasal Symptom Score), disease-specific quality-of-life questionnaires, and peak nasal inspiratory flow. The 3 studies that compared butterbur with nonsedating antihistamines demonstrated no difference between butterbur and antihistamines in the aforementioned outcomes. No trial was longer than 2 weeks.[1]

A 2005 double-blind RCT with 330 adults was the largest single trial in the systematic review and informs on magnitude of effect for butterbur.[2] Butterbur 8 mg 3 times daily was compared with placebo 3 times daily and fexofenadine 180 mg once daily plus placebo twice daily over a 2-week period. Outcome measures included total symptom score (TSS); a subjective assessment consisting of the sum of individual symptoms for sneezing, rhinorrhea, itchy palate/nose/throat, itchy/watery/red eyes, and nasal congestion on a scale of 0 (no symptoms) to 4 (severe symptoms), with a maximum possible score of 20. Other measures included responder rates (50% improvement in TSS at endpoint relative to baseline) and physician assessment using instruments that were not described.

Butterbur was associated with a 3.9-point improvement in TSS compared with a 0.4-point improvement for placebo ($P<.0001$). There was a 32% responder rate with butterbur compared with a 5% responder rate with placebo ($P<.0001$; number needed to treat [NNT]=4). Physicians assessed a full recovery in 31% of patients receiving butterbur compared with 13% of patients receiving placebo ($P<.0001$; NNT=6). No significant differences were found between butterbur and fexofenadine in any of the outcome measures. The authors noted that unpurified butterbur contains pyrrolizidine alkaloids, which have hepatotoxic properties.[2]

A 2011 double-blind, randomized crossover study of 18 adults compared butterbur 20 mg daily with desloratadine (unspecified dose) taken once daily and placebo.[3] Each patient randomly received an intervention for 5 days followed by an allergen challenge, assessment, and washout period. Patients then received a different intervention until all patients had received all interventions. A subjective global nasal assessment score consisting of a 0- to 10-point visual analog scale for sneezing, itching, nasal obstruction, and rhinorrhea was used.

Mean time to return to baseline nasal function after allergen challenge was significantly shorter among participants treated with butterbur (mean 3.2 hours) than participants given desloratadine (mean 4.5 hours; $P=.030$) or placebo (mean 8.3 hours; $P=.027$).[3] EBP

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**REFERENCES**

1. Guo R, Pittler MH, Ernst E. Herbal medicines for the treatment of allergic rhinitis: a systematic review. *Ann Allergy Asthma Immunol*. 2007; 99(6):483–495. **[STEP 1]**
2. Schapowal A. Treating intermittent allergic rhinitis: a prospective, randomized, placebo and antihistamine-controlled study of butterbur extract Ze 339. *Phytother Res*. 2005; 19(6):530–537. **[STEP 2]**
3. Dumitru AF, Shamji M, Wagenmann M, Hindersin S, Scheckenbach K, Greve J, et al. Petasol butenoate complex (Ze 339) relieves allergic rhinitis-induced nasal obstruction more effectively than desloratadine. *J Allergy Clin Immunol*. 2011; 127(6):1515–1521. **[STEP 2]**

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# EVIDENCE-BASED PRACTICE

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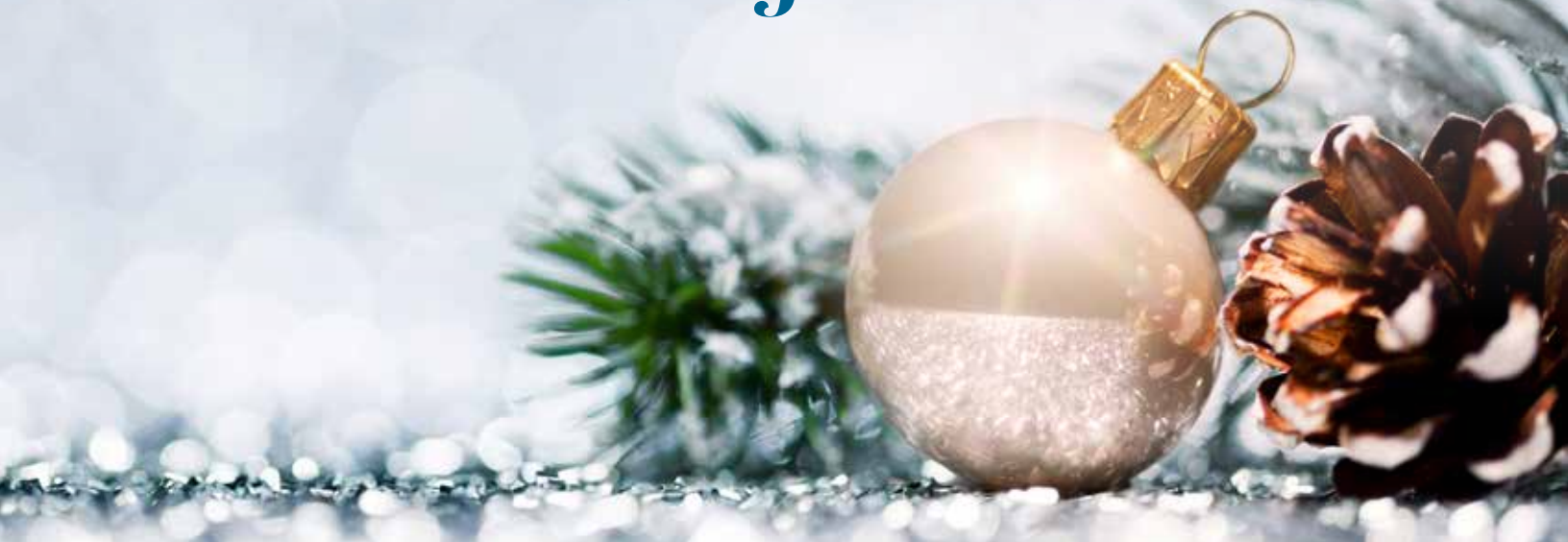

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# EVIDENCE-BASED PRACTICE

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## How do pharmacologic and behavioral therapies compare for the treatment of insomnia?

### EVIDENCE-BASED ANSWER

Pharmacotherapy with benzodiazepines and benzodiazepine receptor agonists show similar efficacy to behavioral therapies for the short-term treatment of chronic insomnia (SOR: **B**, meta-analysis not limited to RCTs). Between drug classes, minimal differences have been found for sleep-onset latency, favoring benzodiazepines over benzodiazepine receptor agonists and antidepressants (SOR: **A**, meta-analysis of RCTs). Cognitive behavioral therapy and benzodiazepine receptor agonists are recommended for short-term treatment of insomnia over other agents (SOR: **C**, expert opinion).

In 2002, a meta-analysis compared pharmacotherapy and behavioral therapy for the treatment of primary insomnia.[1] Twenty-one studies (type not reported) of more than 1 month's duration were included with 470 patients between 21 and 69 years of age diagnosed with initial insomnia, sleep maintenance insomnia, and mixed insomnia. Studies evaluated only pharmacologic therapies with benzodiazepines or benzodiazepine receptor agonists (7 trials, n=203), only behavioral interventions of stimulus control therapy and sleep restriction (13 trials, n=232), or a comparison of pharmacotherapy and behavioral therapy (1 trial, n=35). Treatment duration ranged from 1 to 10 weeks. Outcomes were measured by sleep diaries: sleep latency, total sleep time, number of awakenings, and sleep quality.

Both pharmacologic and behavioral treatments were associated with improvement in outcomes, with no significant differences between treatments. Sleep latency was reduced by 30% with pharmacologic treatment and 43% with behavioral interventions. Wake time after sleep onset was reduced by 46% with pharmacotherapy and 56% with behavior therapy. Total sleep time increased by 12% with pharmacotherapy and 6% with behavior therapy. Pharmacotherapy improved sleep quality (measured on various scales) by 20% and behavior therapy improved sleep quality by 28%.[1]

In 2014 a meta-analysis of placebo-controlled RCTs of middle-aged men and women with a documented history of insomnia evaluated pharmacologic treatment of primary insomnia.[2] Four separate analyses were conducted: any pharmacologic treatment (31 trials, n=3,820), benzodiazepine treatment alone (7 trials, n=152), benzodiazepine receptor agonist (BRZA) treatment alone (17 trials, n=851), and antidepressant treatment alone (6 trials, n=351). Treatment duration in most studies was less than 3 months. Outcomes included both polysomnographic and subjectively measured total sleep time, sleep-onset latency, wake after sleep onset, and sleep efficiency. Results were reported as effect sizes.

For any pharmacologic treatment compared with placebo, the effect sizes for the 8 outcomes were small but significant, ranging from 0.21 to 0.41 ($P<.01$ for all comparisons with placebo). To compare drug classes, the Q statistic was calculated to determine ratio of expected to observed heterogeneity. Benzodiazepines were judged to be significantly more effective than BRZAs for subjective sleep-onset latency (Q statistic 7.8; $P<.001$) and both benzodiazepines and BRZAs were judged to be better than antidepressants for polysomnographic sleep-onset latency (Q statistic 4.4 and 6.7, respectively; $P<.05$). No significant differences were noted between drug classes for the other outcomes.[2]

The National Institute of Health Consensus Development Program released a panel statement in 2005 on the treatment of chronic insomnia based on a systematic review of the medical literature.[3] The panel looked at various treatments including cognitive behavioral therapy, benzodiazepine receptor agonists, antidepressants, and various over-the-counter medications such as melatonin, alcohol, L-tryptophan, valerian, and alcohol.

The panel concluded that evidence supported cognitive behavioral therapy and benzodiazepine receptor agonists for the short-term treatment of insomnia. The panel noted limitations in the research, given that insomnia is a potential lifelong illness and the longest clinical trial lasted at most 1 year.[3]

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1. Smith MT, Perlis ML, Park A, Smith MS, Pennington J, Giles DE, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *Am J Psychiatry*. 2002; 159(1):5–11. **[STEP 1]**
2. Winkler A, Auer C, Doering BK, Rief W. Drug treatment of primary insomnia: a meta-analysis of polysomnographic randomized controlled trials. *CNS Drugs*. 2014; 28(9):799–816. **[STEP 1]**
3. National Institutes of Health. Chronic insomnia. NIH State-of-the-Science Conference on manifestations and management of chronic insomnia in adults. Final panel statement. https://consensus.nih.gov/2005/insomniastatement.htm. Published 2005. Accessed November 9, 2017. **[STEP 5]**

## Is acupuncture effective in treating peripheral neuropathy?

### EVIDENCE-BASED ANSWER

In patients with peripheral neuropathy, acupuncture may produce a small improvement in symptoms compared with sham acupuncture (SOR: **C**, small, conflicting RCTs). No data on functional outcomes are available.

A 2014 single-blinded, placebo-controlled pilot study randomized 45 adults with diabetic peripheral neuropathy to 10 weeks of once-weekly sham or authentic acupuncture.[1] Patients were 18 to 80 years old with type 1 or 2 diabetes and receiving prescription medications for diabetic neuropathy. Authentic acupuncture was performed on 5 standardized acupuncture points on each leg and foot. Sham acupuncture was performed with a blunt needle that did not penetrate the skin.

The following outcomes were evaluated: lower extremity pain intensity using a 100-mm visual analog scale (VAS), changes in health over time using the Measure Yourself Medical Outcome Profile (MYMOP), sleep quality using Sleep Problem Scale, and general health status using the Short Form-36 Health Survey. The MYMOP is a self-assessment symptom questionnaire individualized to include symptoms important to the patient with scores ranging from 0 (no symptoms) to 6 (worst symptoms).[1]

Over the 10-week treatment period, true acupuncture decreased MYMOP score 0.85 points more than sham acupuncture (95% CI, 0.3–1.4), but had no effect on the other outcomes. This study was limited by inadequate participant blinding.[1]

In a 2010 randomized, placebo-controlled pilot study, 63 patients diagnosed with diabetic peripheral neuropathy were randomized in a 2:1 ratio to 15 days of either acupuncture or sham treatment.[2] All 63 patients received daily 30-minute sessions to 5 areas of the body with a total of 10 acupoints needled. For the 42 patients who received true acupuncture, the needles were inserted to a depth of 1.2 to 2.3 cm and rotated every 5 minutes. For the 21 patients in the sham group, the needles were inserted to a depth of 0.3 cm and not rotated. Subjective symptoms were measured by a scoring system rating severity and extent of numbness, pain, and rigidity on a 0 (none) to 4 (severe) scale.

Acupuncture led to statistically greater improvement in severity and extent of numbness, pain, and rigidity. Results were reported only in graphical form, but it appeared that the differences at 15 days ranged from less than 0.1 for severity of numbness and rigidity and extent of numbness and pain to about 0.6 for severity of pain.[2]

A Chinese trial randomized 65 patients (age range 36–68 years) with a diagnosis of diabetes and neuropathy into either a treatment group given 14 sessions of daily acupuncture for 5 consecutive sessions with a 4-day break between sessions or a control group given oral inositol (2 g 3 times daily) for 3 months.3 The patients were assessed with unspecified subjective and objective ratings into 3 categories: markedly relieved, improved, and failed.

In the acupuncture group compared with the control group, 16 versus 7 cases were markedly relieved, 12 versus 14 cases improved, and 4 versus 12 cases failed, with a total effective rate (markedly relieved and improved patients) of 88% in the acupuncture group versus 64% in the control groups ($P<.05$).

Lack of blinding and clarity of outcome measurements limits the validity of this study.[3]

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1. Garrow AP, Xing M, Vere J, Verrall B, Wang L, Jude EB. Role of acupuncture in the management of diabetic painful neuropathy (DPN): a pilot RCT. *Acupunct Med*. 2014; 32(3):242–249. **[STEP 2]**
2. Tong Y, Guo H, Han B. Fifteen-day acupuncture treatment relieves diabetic peripheral neuropathy. *J Acupunct Meridian Stud*. 2010; 3(2):95–103. **[STEP 2]**
3. Zhang C, Ma YX, Yan Y. Clinical effects of acupuncture for diabetic peripheral neuropathy. *J Tradit Chin Med*. 2010; 30(1):13–14. **[STEP 2]**

## Is steroid injection superior to conservative management for the treatment of plantar fasciitis?

### EVIDENCE-BASED ANSWER

Steroid injection is superior to placebo injection and conservative therapies (joint mobilization, stretching, or oral analgesics) for short-term (<12 weeks) pain relief of plantar fasciitis. Steroid injection is not superior to the combined therapy of NSAIDs, soft insoles, stretching, ultrasound therapy, and contrast baths. Plantar fascia rupture is a rare adverse event associated with steroid injections (SOR: **B**, systematic review of RCTs and RCTs with conflicting results).

A 2015 systematic review included 2 RCTs comparing steroid injection with placebo injection for the treatment of plantar fasciitis of at least 8 weeks' duration.[1]

A 2012 RCT (N=82) compared ultrasound-guided injection of 1 mL of 4 mg/mL dexamethasone with ultrasound-guided injection of 1 mL normal saline in nonpregnant patients without a history of trauma, previous steroid injection within the past 6 months, or systemic inflammatory disease. Pain was assessed using the pain domain of the Foot Health Status Questionnaire (FHSQ), scored 0 to 100, with higher scores representing less pain. Steroid injection improved pain at 4 weeks (mean difference 11 points; *P*=.03) but not at 12 weeks compared with placebo.[1]

A 2013 RCT (N=65) compared ultrasound-guided injection of 20 mg methylprednisolone with ultrasound-guided injection of 1 mL normal saline in patients who had failed conservative therapy but who did not have inflammatory arthritis, prior heel surgery, previous trauma, or previous steroid injection of the heel. Pain was assessed on a 0-to-100 visual analog scale (VAS). Steroid injection improved pain at 6 weeks (mean difference 19.7 points; *P*=.03) and 12 weeks (mean difference 25.1 points; *P*=.009) compared with placebo. No adverse events were reported in either study.[1]

A 2016 RCT (N=43) compared 9 sessions of joint mobilization and stretching with a 40-mg methylprednisolone steroid injection for the treatment of plantar fasciitis in patients aged 30 to 60 years without rheumatologic or neurologic disease.[2] Participants had an average duration of symptoms of 11 months in the mobilization and stretching group and 13 months in the injection group. Pain was assessed on a 0-to-10 VAS, and function was measured using the Foot and Ankle Ability Measure (FAAM, scale 0–112, higher scores indicate higher function).

Steroid injection improved pain and function more than joint mobilization and stretching at 3, 6, and 12 weeks, with a mean difference for pain at 12 weeks of 3.4 points (*P*=.001), and a mean difference for function of 14 points (*P*=.008). However, no difference in pain or function was seen between the groups at 1 year. No adverse effects were reported.[2]

A 2014 RCT (N=200) compared weekly (up to 3 total) unguided injections of 40 mg methylprednisolone mixed with 1 mL 2% lidocaine versus conservative therapy (combined NSAIDs, soft insoles, stretching, ultrasound therapy, and contrast baths) for the treatment of nontraumatic heel pain of at least 2 weeks' duration in nonpregnant patients aged 18 to 65 years.[3] Pain was evaluated using a 0-to-100 VAS.

No difference was noted between steroid injection and conservative therapy at 4 and 8 weeks. No adverse effects were noted. A limitation of this study was the short follow-up period.[3]

A 2011 RCT (N=120) compared unguided injection of 40 mg methylprednisolone mixed with 2 mL 0.5% bupivacaine versus oral analgesics (diclofenac 50 mg BID plus paracetamol 500 mg BID) for the treatment of plantar fasciitis of less than 3 months' duration in patients aged 25 to 60 years without significant systemic disorder or previous treatment.[4] Pain was assessed using a 0-to-10 VAS.

Steroid injection resulted in lower pain scores than oral analgesics at week 1 (2.0 vs 5.1), week 2 (1.1 vs 4.8), week 4 (1.1 vs 4.2), and week 8 (1.9 vs 5.8; *P*<.01 for all time

comparisons). The most common adverse events were gastritis and esophagitis (45 of 60 participants in the oral analgesic group vs 0 of 60 participants in the steroid group). Two plantar fascia ruptures were observed in the steroid injection group.[4]

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1. Landorf K. Plantar heel pain and plantar fasciitis. *BMJ Clin Evid*. 2015 Nov 25; 2015. pii: 1111. **[STEP 1]**
2. Celik D, Kuş G, Sirma SÖ. Joint mobilization and stretching exercise vs steroid injection in the treatment of plantar fasciitis: a randomized controlled study. *Foot Ankle Int*. 2016; 37(2):150–156. **[STEP 2]**
3. Narula R, Iraqi AA, Narula K, Katyal R, Saxena MS. Comparative study of: non-invasive conservative treatments with local steroid injection in the management of plantar fasciitis. *J Clin Diagn Res*. 2014; 8(9):LC05–LC07. **[STEP 2]**
4. Biswas C, Pal A, Acharya A. A comparative study of efficacy of oral nonsteroidal antiinflammatory agents and locally injectable steroid for the treatment of plantar fasciitis. *Anesth Essays Res*. 2011; 5(2):158–161. **[STEP 2]**

## In pregnant women, do docosahexaenoic acid (DHA) supplements lead to any differences in early childhood developmental outcomes?

### EVIDENCE-BASED ANSWER

DHA supplementation in pregnant women does not appear to lead to any consistent differences in early childhood cognitive, motor, or language development (SOR: **B**, RCTs with conflicting results).

A 2013 systematic review of 11 RCTs with 5,272 women evaluated the effects of prenatal and infant supplementation of omega-3 long-chain polyunsaturated fatty acids (including DHA) versus placebo vegetable oil on cognitive development in children.[1] Two trials evaluated DHA supplements given during pregnancy only.

In 1 RCT (n=726) 800 mg DHA supplement was given daily from weeks 18 to 21 of pregnancy to birth. Cognitive and motor development was measured at 12 to 24 months with the Bayley Scales of Infant and Toddler Development III and the Griffiths Mental Development Scales. Language was measured by Bayley Scale and the Peabody Picture Vocabulary Test.[1]

No significant differences were noted in cognitive, motor, or language development for children whose mothers were given DHA supplementation versus placebo during pregnancy. Fewer toddler-aged children had delayed cognitive development (using the common definition of Bayley Scale score <85) in the treatment group than in the control group (2.7% vs 6.6%; statistical analysis not reported).[1]

The second RCT (n=72) evaluated 2,200 mg DHA given daily from 20 weeks of pregnancy to birth using the Griffiths Mental Development Scales and Peabody Picture Vocabulary Test to assess cognition and language at 2 to 5 years. No difference was found in outcomes between the DHA and placebo groups. This trial had moderate bias because of high attrition and unclear randomization.[1]

A 2007 RCT evaluated the infants of 29 women aged 18 to 25 years given either DHA-containing cereal-based bars (300 mg DHA/bar, average consumption 5 bars/week, average DHA consumption of 214 mg/d) or placebo cereal bars from gestation week 24 until delivery.[2] This trial was included in the above systematic review, but was not used in any of the analyses reported above. The problem-solving and recognition memory abilities of the infants were evaluated at 9 months of age. Problem-solving was assessed by evaluating the infant's ability to execute a series of steps to retrieve a toy. Recognition memory was assessed by the Fagan Test of Infant Intelligence, in which the number of times an infant looks at familiar and novel cards is measured along with the total time looking at the card.

The infants in the DHA group were able to successfully uncover the toy more often than the placebo group (mean number of solutions 3.4 and 2.3, respectively; *P*=.008). No significant difference was noted in the Fagan Test between the DHA and placebo groups.[2]

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1. Gould JF, Smithers LG, Makrides M. The effect of maternal omega-3 (n-3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2013; 97(3):531–544. **[STEP 2]**
2. Judge MP, Harel O, Lammi-Keefe CJ. Maternal consumption of a docosahexaenoic acid-containing functional food during pregnancy: benefit for infant performance on problem-solving but not on recognition memory tasks at age 9 mo. *Am J Clin Nutr*. 2007; 85(6):1572–1577. **[STEP 2]**

## What is the most effective nonsurgical therapy for lower leg intermittent claudication?

### EVIDENCE-BASED ANSWER

Exercise therapy has the most consistent benefit for increasing both maximum (by >100 meters) and pain-free (by 39–82 meters) walking distances compared with usual therapy (SOR: **A**, 2 meta-analyses). Cilostazol does not improve mean walking distance when compared with usual therapy, although both therapies improve quality of life (SOR: **A**, meta-analysis). Anticoagulant drugs show no clinical benefit (SOR: **A**, meta-analysis).

A 2014 systematic review of 30 RCTs (N=1,816) assessed the effects of exercise on patients with stable leg pain due to intermittent claudication.[1] Exercises included strength training, cycling, pole-striding, and upper or lower limb exercises for 2 or more sessions per week. Trial quality was considered moderate, with most trials consisting of 20 to 49 patients followed for 2 weeks to 2 years.

Twenty-five trials (n=1,674) compared exercise with usual care or placebo medication; 7 (n=447) compared exercise with either medication (pentoxifylline, iloprost, antiplatelet agents, or vitamin E) or pneumatic calf compression; 2 studies (n=305) included both usual care and active treatment comparators.[1]

Exercise improved maximal walking time compared with usual care or placebo, with a mean difference (MD) of 4.5 minutes (12 trials, n=577; 95% CI, 3.1–5.9). Walking distances were also better: pain-free distance increased by a mean of 82 meters (8 trials, n=371; 95% CI, 72–93), and maximum distance by a mean of 109 meters (9 trials, n=480; 95% CI, 38–180). Comparisons of exercise with medications or pneumatic calf compression were inconclusive because of the small numbers of trials and participants.[1]

A 2015 meta-analysis of 27 RCTs (7,475 patients) funded by the Agency for Healthcare Research and Quality evaluated comparative effectiveness of medical therapy, supervised exercise, and revascularization to improve walking and quality of life in patients with intermittent claudication.[2] Three trials (n=378) were included in the 2014 systematic review mentioned above. Patients were at least 18 years old with ankle-brachial index less than 0.9 and symptomatic claudication. Study quality was assessed as good in 12 (44%), fair in 13 (48%), and poor in 2 (7%).

Only supervised exercise training (type not defined) improved both maximal walking distance (6 trials, n=467; mean difference 150 meters; 95% CI, 35–266) and initial claudication distance (4 trials, n=162; MD 39 meters; 95% CI, 9–65) in relation to usual care. Cilostazol did not increase maximal walking distance or initial claudication distance. All treatment modalities showed small improvements in quality of life versus usual care. On the Short Form-36 (0–100 scale), again compared with usual care, physical functioning scores improved a mean of 4.4 points more for cilostazol (95% CI, 0.5–8.3) and 5.6 points more for exercise training (95% CI, 2.5–8.6); however, no differences were noted between therapies in terms of comparative improvement. Data were insufficient to assess treatment-related complications, and there was no difference in all-cause mortality between therapies.[2]

A 2014 systematic review of 7 RCTs (N=802) assessed the effects of anticoagulant drugs (heparin, low-molecular-weight heparin, and oral anticoagulants) in patients with intermittent claudication (leg pain and weakness brought on by walking, with resolution after a brief rest).[3] Outcome measures were walking capacity (pain-free walking distance or absolute walking distance), mortality, cardiovascular events, ankle-brachial index, progression to surgery, amputation-free survival, and medication adverse events.

No study showed benefit of anticoagulant drugs for any primary outcome. Major and minor bleeding events were more common with oral anticoagulants than in the control group. The increase in minor bleeding events with heparin versus control was not significant.[3]

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1. Lane R, Ellis B, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2014; (7): CD000990. **[STEP 1]**
2. Vemulapalli S, Dolor RJ, Hasselblad V, Subherwal S, Schmit KM, Heidenfelder BL, et al. Comparative effectiveness of medical therapy, supervised exercise, and revascularization for patients with intermittent claudication: a network meta-analysis. *Clin Cardiol*. 2015; 38(6):378–386. **[STEP 1]**
3. Cosmi B, Conti E, Coccheri S. Anticoagulants (heparin, low molecular weight heparin and oral anticoagulants) for intermittent claudication. *Cochrane Database Syst Rev*. 2014; (5):CD001999. **[STEP 1]**

## What are the diagnostic criteria for interstitial cystitis?

### EVIDENCE-BASED ANSWER

Interstitial cystitis may be diagnosed by the more restrictive criteria of the National Institute of Diabetes, Digestive, and Kidney (NIDDK), which requires bladder pain or urinary urgency for 9 months, the presence of glomerulations or Hunner's ulcer on cystoscopy, and urodynamic evaluation. The NIDDK criteria exclude more than 50% of patients who clinicians suspect have interstitial cystitis based on the more inclusive criteria of urinary frequency (≥7 times per day), urgency, or bladder pain for at least 6 months with no other clear etiologies (SOR: **B**, cross-sectional study). The most common symptoms of interstitial cystitis include urgency, frequency, nocturia, pain in the bladder, pain in the urethra, and pain in the vagina (SOR: **B**, systematic review of cross-sectional studies). Experts characterize interstitial cystitis as an unpleasant sensation (pain, pressure, discomfort) thought to be related to the urinary bladder and associated with lower urinary tract symptoms of more than 6 weeks' duration, in the absence of infection or other identifiable causes (SOR: **C**, expert opinion).

A cross-sectional study of 379 woman who were enrolled in the Interstitial Cystitis Database (ICDB) evaluated the utility of the NIDDK criteria as a diagnostic tool for interstitial cystitis, compared the restrictive requirements of the NIDDK criteria versus the more inclusive ICDB criteria.[1] The patients were enrolled in the ICDB if they were 18 or older with urinary frequency (≥7 times per day), urgency, or bladder pain for at least 6 months and had no other clear etiologies such as infection, calculi, stricture, cancer, or radiation treatments. Based on these criteria and other available clinical information, study physicians classified these patients as either definitely, very likely, possibly, not very likely, or definitely not likely to have interstitial cystitis.

Investigators then applied the NIDDK criteria to the patients: bladder pain or urinary urgency for at least 9 months in patients 18 or older and cystoscopy criteria of Hunner's ulcer or bladder glomerulations. The NIDDK excludes patients with fewer than 8 voids per day; without nocturia; with history of symptom relief from antibacterials, anticholinergics, or antispasmodics; with any other possible etiology for symptoms; and cystoscopy/urodynamics criteria of bladder volume more than 350 mL; involuntary bladder contractions, and absence of intense urge to void with bladder filled to 150 mL.[1]

Of the 269 women classified by investigators to definitely/very likely have interstitial cystitis based on the ICDB criteria, only 32% met the full NIDDK criteria and 42% met the noninvasive NIDDK criteria. Of the 118 women who met the noninvasive NIDDK criteria, 87% were classified as definitely/very likely based on the ICDB criteria.[1]

A 2007 systematic review evaluated the symptoms most commonly associated with interstitial cystitis.[2] Studies of patients with bladder cancer, bladder stones, or exposure to cyclophosphamide or radiation were excluded. Six cross-sectional studies with 100 or more patients, mostly females, were included but criteria used to diagnose interstitial cystitis in these studies were not reported.

Symptoms reported by at least 50% of patients were urgency (84%–98%), urinary frequency (80%–92%), nocturia (61%–89%), pain in any location (63%–92%), pain in the bladder (55%–71%), pain in the urethra (50%–74%), and pain in the vagina (51%–61%). A significant flaw was the reliance on self-reporting used in the studies.[2]

The 2014 guideline from the American Urological Association (AUA) provides recommendations for the diagnosis of interstitial cystitis based on a systematic literature review, but with the diagnostic algorithm developed through consensus opinion.[3] The guideline stated that in the absence of infection or other identifiable causes, interstitial cystitis presents as an unpleasant sensation (pain, pressure, discomfort) thought to be related to the bladder for more than 6 weeks' duration. The AUA recommended cystoscopy and urodynamic testing when the diagnosis is uncertain.

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1. Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg L Jr. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. *J Urol*. 1999; 161(2):553–557. **[STEP3]**
2. Bogart LM, Berry SH, Clemens JQ. Symptoms of interstitial cystitis, painful bladder syndrome and similar diseases in women: a systematic review. *J Urol*. 2007; 177(2):450–456. **[STEP 3]**
3. American Urological Association. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. Guideline summary. Linthicum, MD: American Urological Association Education and Research, Inc. http://www.auanet.org/guidelines/interstitial-cystitis/bladder-pain-syndrome-(2011-amended-2014). Published 2011; amended 2014. Accessed November 9, 2017. **[STEP 5]**

## What is the optimal dose of vitamin D in patients with osteoporosis?

### EVIDENCE-BASED ANSWER

The answer is unclear. For daily dosing in patients older than 64 years, 792 to 2,000 IU vitamin D per day decreases the risk of hip fracture by 30% and nonvertebral fracture by 14% compared with placebo (SOR: **A**, meta-analysis RCTs). For monthly dosing in elderly patients with a prior fall, 24,000 IU vitamin D leads to a lower incidence of falls at 1 year compared with higher monthly doses of vitamin D 60,000 IU or vitamin D 24,000 IU plus 300 µg calcifediol, but the effect compared with placebo is not known (SOR: **B**, single RCT).

A 2012 meta-analysis of 11 double-blinded RCTs (N=31,022) compared fracture risk in patients 65 years old or older (91% women) who received oral vitamin D supplementation (n=15,527) with individuals who took calcium alone (averaging 84–830 mg daily) or placebo (n=15,495).[1] Of the 11 RCTs, 8 trials combined calcium intake in the vitamin D treatment groups and all trials giving at least 800 IU/d vitamin D also allowed calcium supplementation.

Oral vitamin D supplementation was given daily, weekly, or every 4 months, averaging between 192 and 1,026 IU/d. In 5 of the studies, control groups were allowed vitamin D supplementation of less than 400 IU/d (mean 100 IU/d) with or without calcium (mean 84 mg/d). Vitamin D dosages were stratified into quartiles: 0–360 IU/d (n=3,936), 361–637 IU/d (n=3,836), 638–791 IU/d (n=3,790), and 792–2,000 IU/d (n=3,966). Primary outcomes included the risk of hip and nonvertebral fractures adjusted for variables such as age group, sex, and dwelling type.[1]

Only vitamin D intake in the highest quartile group, 792–2,000 IU/d, decreased the risk of hip fracture (hazard ratio [HR] 0.7; 95% CI, 0.58–0.86) and the risk of nonvertebral fractures (HR 0.86; 95% CI, 0.76–0.96) compared with placebo, regardless of calcium intake.[1]

A 2016 RCT (N=200) examined the effects of different doses of vitamin D on function over 1 year. The study evaluated community-dwelling individuals with a prior fall (>70 years old and 67% female) randomized into 3 groups treated monthly with vitamin $D_3$ 24,000 IU, vitamin $D_3$ 60,000 IU, or vitamin $D_3$ 24,000 IU plus 300 µg calcifediol (a liver metabolite of vitamin D).[2] There was no placebo group. Primary outcomes were lower extremity function based on the Short Physical Performance Battery (SBBP; scored 1–12, with higher scores representing better function) and percent of patients with a serum 25(OH)-vitamin D level of at least 30 ng/mL. The secondary outcome measure was frequency of falls.

Lower extremity function did not significantly differ among the 3 groups. Groups receiving 60,000 IU vitamin $D_3$ and 24,000 IU vitamin $D_3$ plus calcifediol compared with the

**TABLE**

**Effects of different doses of vitamin D on limb function, serum 25(OH)-vitamin D levels, and falls[2]**

| Monthly vitamin $D_3$ dose | SBBP score increase from baseline to 1 year (95% CI) | Patients with serum 25(OH)-vitamin D ≥30 ng/mL, % (95% CI) | Incidence of falls at 1 year, % (95% CI) | Mean number of falls at 1 year (95% CI) |
|---|---|---|---|---|
| 24,000 IU | 0.38 (0.07 to 0.68) | 55 (42 to 67) | 48 (36 to 60) | 0.94 (0.6 to 1.3) |
| 24,000 IU + 300 µg calcifediol | 0.11 (–0.19 to 0.43) | 83[a] (71 to 91) | 66[b] (54 to 77) | 1.2 (0.89 to 1.6) |
| 60,000 IU | 0.1 (–0.21 to 0.41) | 81[a] (69 to 89) | 67[b] (54 to 78) | 1.5 (1.1 to 1.8) |

[a]Significantly better than the 24,000 IU vitamin D3 group (*P*=.001).

[b]Significantly worse than the 24,000 IU vitamin D3 group (*P*=.048).

SBBP=Short Physical Performance Battery.

24,000 IU group were more likely to achieve serum 25(OH)-vitamin D levels of more than 30 ng/mL, but they also had a higher incidence of falls at 1 year, even though the mean number of falls did not differ significantly (see **TABLE**).[2]

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1. Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. *N Engl J Med*. 2012; 367(1):40–49. **[STEP 1]**
2. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. *JAMA Intern Med*. 2016; 176(2):175–183. **[STEP 2]**

## Is autologous blood injection more effective than corticosteroid injections for lateral epicondylitis?

### EVIDENCE-BASED ANSWER

Yes, at least after 6 weeks. For patients with lateral epicondylitis, autologous blood injections improve pain and function more than corticosteroid injections after 6 weeks, but in the short term provide less or equivalent symptom relief (SOR: **A**, meta-analysis of RCTs and individual RCTs).

A meta-analysis in 2015 of 10 RCTs included 3 studies (N=180) that compared autologous blood with corticosteroid injections for the treatment of lateral epicondylitis.[1] Two studies used a 10-point visual analog scale (VAS), 1 study used the 100-point Disabilities of Arm, Shoulder, and Hand (DASH) score (not described), and 1 study used the Patient-Rated Tennis Elbow Evaluation score (PRTEE) to evaluate pain and function. The PRTEE is a 15-item questionnaire with scores ranging from 0 (best score) to 100 (worst score). The autologous blood preparations combined blood and lidocaine or bupivacaine. The steroid preparations were not described.

At 2- to 6-month follow-up, autologous blood was superior to steroid injections for pain and function. VAS scores improved a mean of 2.5 points (2 trials, n=120; 95% CI, 1.5–3.5), DASH scores improved a mean of 26 points (1 trial, n=60; 95% CI, 17–34), and PRTEE scores improved a mean of 5.3 points (1 trial, n=60; 95% CI, 1.6–9.1). The risk of adverse effects was higher with autologous blood than corticosteroid injections (1 trial, n=120; RR 1.8; 95% CI, 1.0–3.1), but the details of these effects were not provided.[1]

A 2014 RCT (not included in above meta-analysis) compared injections of autologous blood versus steroid injections in 80 patients with lateral epicondylitis.[2] Patients were randomized to autologous blood (2 mL blood with 1 mL 2% prilocaine hydrochloride) or 40 mg methylprednisolone with 1 mL 2% prilocaine. Pain (VAS, scale 0–10) was followed for 180 days and pain and function (PRTEE score) was followed for 90 days.

At 15 days, steroid therapy compared with blood injections had lower absolute VAS scores (1.7 vs 5.3, respectively; *P*=.0001) and PRTEE scores (20 vs 51, respectively; *P*=.0001). But at 90 days, blood was superior to steroids, culminating in VAS scores at 180 days of 0.06 and 2.7, respectively (*P*=.0001). Similarly, at 90 days, blood was superior to steroid injection at reducing PRTEE scores (19 vs 35; *P*=.0001). Autologous blood compared with steroid injections had a higher rate of complete recovery (defined as a 37% decrease in PRTEE) at 3 months (95% vs 25%; *P*=.0001).[2]

In 2013 a single-blinded RCT (N=50, not included in above meta-analysis) compared autologous blood (2 mL venous blood with 1 mL 2% lidocaine) and 40 mg methylprednisolone with 1 mL 2% lidocaine injections for the treatment of lateral epicondylitis.[3] Patients were evaluated at 2 and 6 weeks for pain (VAS, scale 0–10) and disability (Nirschl staging: 1 mild pain with exercise through 7 constant pain).

Autologous blood and steroid injections were similar at 2 weeks (VAS 4.2 vs 3.5, *P*=.082; and Nirschl 3.5 vs 3.2, *P*=.436), but at 6 weeks autologous blood injections were superior (VAS 1.5 vs 2.3, *P*=.0396; and Nirschl 1.4 vs 2.4, *P*=.0045).[3]

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1. Arirachakaran A, Sukthuayat A, Sisayanarane T, Laoratanavoraphong S, Kanchanatawan W, Kongtharvonskul J. Platelet-rich plasma versus autologous blood versus steroid injection in lateral epicondylitis: systematic review and network meta-analysis. *J Orthop Traumatol*. 2016; 17(2):101–112. **[STEP 1]**
2. Arik HO, Kose O, Guler F, Deniz G, Egerci OF, Ucar M. Injection of autologous blood versus corticosteroid for lateral epicondylitis: a randomised controlled study. *J Orthop Surg (Hong Kong)*. 2014; 22(3):333–337. **[STEP 2]**
3. Jindal N, Gaury Y, Banshiwal RC, Lamoria R, Bachhal V. Comparison of short term results of single injection of autologous blood and steroid injection in tennis elbow: a prospective study. *J Orthop Surg Res*. 2013; 8:10. **[STEP 2]**

## Does home blood pressure monitoring aid in the management of patients with hypertension?

### EVIDENCE-BASED ANSWER

Home blood pressure monitoring (HBPM) is associated with reductions in systolic blood pressure (SBPs) and diastolic blood pressures (DBPs), ranging from 2.6–3.1 mmHg and 1.7–2 mmHg, respectively, for at least 6 months when compared with office-based blood pressure monitoring (OBPM) (SOR: **C**, systematic reviews of RCTs and prospective comparative studies with disease-oriented outcomes). HBPM may further improve BP control when used with some form of additional support (such as counseling, education, web support, behavioral interventions, home visits) or telemonitoring (SOR: **C**, systematic reviews of RCTs and prospective comparative studies with disease-oriented outcome).

A 2012 meta-analysis of 49 prospective studies, 43 RCTs, 3 quasi-RCTs, and 3 nonrandomized studies (total N not provided) evaluated whether HBPM improves BP control compared with usual care (typically any office or clinic BP monitoring) over 2 to 24 months.[1] All patients were adults, most were male, and the most commonly cited comorbid conditions were type 1 or 2 diabetes, obesity, dyslipidemia, and cardiovascular disease.

At 6 months, SBP was lowered by a mean difference of 3.1 mmHg (7 trials, n=1,679; 95% CI, –5 to –1.2 mmHg) and DBP by a mean difference of 2 mmHg (9 trials, n=1,815; 95% CI, –3.2 to –0.8 mmHg) with HBPM compared with usual care. At the 12-month follow-up, the difference in SBP was not significant (7 trials, n=2,236). In 6 high-quality RCTs, HBPM plus additional support (such as counseling, education, web support, behavioral interventions, home visits) was associated with lower BPs (SBP/DPB –3.4 to –8.9 mmHg/–1.9 to –4.4 mmHg) for up to 12 months compared with usual care; a meta-analysis was not performed due to heterogeneity of the data.[1]

A 2011 meta-analysis of 37 RCTs (N=9,446), 32 of which were included in the above study, sought to quantify the magnitude of benefit of HBPM on BP reduction.[2] All patients were adults with mean ages between 47 and 77 years old living in North America, Europe, Australia, and Brazil.

In the HBPM group, SBP was lowered by an average of 2.6 mmHg (95% CI, –4.2 to –1.0) and DBP by 1.7 mmHg (95% CI, –2.6 to –0.8) compared with the OBPM group at 2 to 36 months of follow-up. A subgroup analysis of studies that incorporated telemonitoring, in which BP readings obtained at home were relayed electronically to the provider, a greater improvement was noted in SBP, with a reduction of 3.2 mmHg (5 trials, n=not supplied; 95% CI, –4.66 to –1.73) compared with 1.3 mmHg (17 trials, n=not supplied; 95% CI, –2.20 to –0.31) in the studies that did not include telemonitoring. Limitations of this meta-analysis included significant heterogeneity in design among the studies.[2]

In 2008, the American Heart Association, the American Society of Hypertension, and the Preventive Cardiovascular Nurses Association issued a joint statement supporting the use of HBPM as a routine component of BP measurement in most patients with known or suspected hypertension.[3]

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1. Uhlig K, Balk EM, Patel K, Ip S, Kitsios GD, Obadan NO, et al. Self-measured blood pressure monitoring: comparative effectiveness [Internet]. Comparative Effectiveness Review No. 45. AHRQ publication 12-EHC002-EF. Rockville, MD: Agency for Healthcare Research and Quality. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0040902/. Published January 2012. Accessed October 14, 2017. **[STEP 1]**
2. Agarwal R, Bills JE, Hect TJ, Light RP. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control: a systematic review and meta-analysis. *Hypertension*. 2011; 57(1): 29–38. **[STEP 1]**
3. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D. Call to action on use and reimbursement for home blood pressure monitoring: executive summary. A joint scientific statement from the American Heart Association, American Society of Hypertension, and Preventive Cardiovascular Nurses Association. *J Clin Hypertens (Greenwich)*. 2008; 10(6):467–476. **[STEP 5]**

## How well does C-reactive protein correlate with disease progression in rheumatoid arthritis?

### EVIDENCE-BASED ANSWER

In patients with rheumatoid arthritis (RA), C-reactive protein (CRP) levels moderately correlate with radiographic disease progression at 10 years, while radiographic progression at 1 year is associated with a rise in CRP levels (SOR: **C**, case series and retrospective cohort study). Persistently elevated CRP levels may be useful in predicting need for joint replacement surgery (SOR: **C**, retrospective cohort study).

A 2005 prospective case series assessing the prognostic value of various serum laboratory markers for joint damage in RA enrolled 183 patients with early RA.[1] The primary outcome was hand and foot joint damage evaluated by radiography at 5 and 10 years. Patients with active disease were treated with disease-modifying antirheumatic drugs using accepted clinical practice guidelines. Participants had radiographs performed of the hands and feet to assess a total of 32 joints. Each joint was graded on a 0–5 scale, with a score of 2 or more indicating erosive disease.

Baseline CRP levels were not helpful in predicting scores on year 5 radiographs, but the correlation coefficient of CRP for year 10 radiograph scores was 0.4 (n=128; *P*<.001). The investigators estimated an increase in CRP of 1 mg/L corresponded to an average 0.42 increase in the radiograph score.[1]

A 2016 retrospective analysis of a subset of data from a pharmacotherapy trial evaluated the association between laboratory markers and radiographic disease progression in 220 patients with RA.[2] Researchers measured several disease markers, including joint scores, CRP, erythrocyte sedimentation rate, and a multi-biomarker disease activity score (a calculation based on 12 RA biomarkers). Measurements were made at baseline and at 1 year, and separated into 2 groups based on the presence (n=41) or absence (n=179) of radiographic disease progression (as determined by predefined criteria).

At baseline the mean CRP was 34.5 mg/L; after 1 year, patients without radiographic disease progression had a CRP level of 31.8 mg/L and patients with disease progression had a level of 46.2 mg/L (*P*=.049).[2]

A 2008 retrospective cohort study evaluated the relationship between CRP and likelihood of joint replacement using health information data from 2,421 patients.[3] The researchers obtained health information from a proprietary database of patients followed by general practitioners in the United Kingdom. The study looked for patients with newly diagnosed RA who had an initial CRP and at least 1 follow-up visit with CRP measurement.

The hazard ratio for total joint replacement (n=125) among patients with consistently high CRP (defined as CRP >10 mmol/L) was approximately double that of the comparator group with persistently low CRP values (≤10 mmol/L) (hazard ratio 2.2; 95% CI, 1.0–4.6) with a median time to event of 117 months (interquartile range 71–161 months). No significant difference was noted in the risk of joint replacement between the comparator group and patients who went from low to high CRP or patients who went from high to low CRP.[3] EBP

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*The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense*

1. Lindqvist E, Eberhardt K, Bendtzen K, Heinegård D, Saxne T. Prognostic laboratory markers of joint damage in rheumatoid arthritis. *Ann Rheum Dis*. 2005; 64(2):196–201. **[STEP 4]**
2. Hambardzumyan K, Bolce RJ, Saevarsdoltirs S, Forslind K, Wallman JK, Cruickshank SE, et al. Association of a multibiomarker disease activity score at multiple time-points with radiographic progression in rheumatoid arthritis: results from the SWEFOT trail. *RMD Open.* 2016; 2(1):e000197. **[STEP 3]**
3. Poole CD, Conway P, Reynolds A, Currie CJ. The association between C-reactive protein and the likelihood of progression to joint replacement in people with rheumatoid arthritis: a retrospective observational study. *BMC Musculoskelet Disord*. 2008; 9:146. **[STEP 3]**

## Inhaled isopropyl alcohol for nausea

Beadle KL, Helbling AR, Love SL, April MD, Hunter CJ. Isopropyl alcohol nasal inhalation for nausea in the emergency department: a randomized controlled trial. *Ann Emerg Med*. 2016; 68(1):1–9.e1..

A 2016 RCT of 80 patients presenting to the emergency department with nausea and vomiting compared the antiemetic effectiveness of inhaled isopropyl alcohol versus inhaled normal saline. Patients were a convenience sample of adults 18 to 64 years old complaining of nausea and vomiting.

Patients inhaled isopropyl alcohol or saline through the nose 3 separate times for less than 60 seconds at 0, 2, and 4 minutes. The primary outcome was reduction in nausea, evaluated on an 11-point verbal numeric response scale at 0, 2, 4, 6, and 10 minutes posttreatment. Secondary outcomes were pain reduction (0, 2, 4, 6, and 10 minutes posttreatment) and patient satisfaction at 10 minutes posttreatment.

Patients in the isopropyl alcohol group reported lower verbal numeric response scale nausea scores during every study period compared with the placebo group. Median nausea verbal response scale scores at 10 minutes were lower in the intervention group (6 vs 3; effect size [ES] 3; 95% CI, 2–4). No significant differences were noted between the intervention and placebo in the 10-minute median pain scores (6 vs 6; ES 0; 95% CI, –1 to 2). The intervention group reported higher satisfaction scores (1–5 scale) than the placebo group (2 vs 4; ES 2; 95% CI, 2–2). No significant differences were noted in the percentage of patients receiving rescue antiemetics, number of antiemetic doses, or antiemetic dose amounts between groups (all $P>.05$).

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

**Bottom line:** The use of inhaled isopropyl alcohol for the treatment of nausea is quick, effective, and easy to use with no reported adverse events over 10 minutes. However, the duration of effectiveness is unclear and there ended up being no difference in the use of rescue antiemetics.

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## Virtual reality to prevent falls

Mirelman A, Rochester L, Maidan I, Del Din S, Alcock L, Nieuwhof F, et al. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. *Lancet*. 2016; 388(10050):1170–1182..

This RCT conducted at 5 clinics in 5 countries evaluated the effectiveness of treadmill training with virtual reality in 282 community-living older adults 60 to 90 years old with a high risk of falls (defined as ≥2 falls in the past 6 months). Patients were randomized to 6 weeks of treadmill training alone or treadmill training with virtual reality, which included a camera for motion capture and a computer-generated simulation projected on a screen. This simulation allowed the patient to experience real-life obstacles and distractions that required attention and adjustments of steps.

At 6 months after the training, the incident rate of falls significantly decreased from baseline in the virtual reality group (12 vs 6; $P<.0001$), but not in the treadmill-alone group (11 vs 8.3; $P=.49$). The incident fall rate was significantly lower in the virtual reality group than in the treadmill-alone group at 6 months (incident rate ratio 0.58; 95% CI, 0.36–0.96).

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

**Bottom line:** The addition of virtual reality to treadmill training appears to help decrease the amount of falls in those patients at risk of falling; however, the availability of the equipment and technology within the family medical care setting may limit the implementation of this treatment. EBP

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