

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the
Family Physicians Inquiries Network

EDITORIAL

2 Shoes

IN DEPTH

3 Statins for cardiac surgery

DIVING FOR PURLs

4 Direct oral anticoagulants versus warfarin for atrial fibrillation

Physical therapy versus surgery for meniscal tears

5 Treatment duration for community-acquired pneumonia

Oral contraceptive pills and risk of pulmonary embolism

EBM ON THE WARDS

6 Treating subsegmental pulmonary embolism

HELPDESK ANSWERS

7 Hyaluronic acid versus corticosteroids in the treatment of osteoarthritis of the knee

8 Image-guided glucocorticoid injection for shoulder pain

Do learning disabilities affect ImpACT baseline values?

10 Best treatment for *Giardia*

Maternal use of hair dye and fetal outcomes

11 Naltrexone for fibromyalgia

12 Cognitive risks associated with vitamin B₁₂ deficiency in the elderly

13 Combined oral contraceptives for implant-related uterine bleeding

14 PPE to reduce nosocomial MRSA transmission

SPOTLIGHT ON PHARMACY

15 Spironolactone dose for resistant hypertension

ONLINE CONTENT

E1 Use of allopurinol during acute gouty attack

E2 Statins and elevated hs-CRP

E2 Best screening instrument for panic disorder

E3 Measuring blood pressure of children on ADHD stimulant therapy

E6 Weight loss increases libido in obese men

E7 Probiotics for IBS

E8 Benzodiazepines for anxiety disorder

E9 Calcium and fracture risk

E10 Association of *H pylori* infection with migraine

E11 Topical therapy for acute musculoskeletal pain

E12 Statin therapy for dyslipidemia in obese children

E13 Interventions for chronic or recurrent yeast infections

E14 Effect of psychoeducation in dementia management

View this issue and access the online content at: www.fpin.org/ebparchives

Shoes

I like to go running. Along with all the presumed health benefits of regular exercise, another “benefit” of this pastime is the large collection of old running shoes I now own. After a few months, most running shoes lose tread from the heel and the linings start to rip out, so they no longer protect my feet from high-impact conditions. However, they still do a fine job for walking, gardening, beachcombing, and the like, making it hard for me to ever throw a pair away.

I currently have at least 2 dozen pairs of old running shoes in a large pile in a corner of my garage. I try not to let friends see it, because it always triggers snide comparisons with Imelda Marcos (a Philippine political insider infamous for owning more than 3,000 pairs of shoes). When people see my shoe pile, I must defend my frugality while they are judging my extravagance.

With great humility, then, and with full awareness of the unfair derision that shoe choices can generate, I wanted to share an interesting study about shoes—specifically high-heeled shoes. Researchers reviewed records from a random sample of emergency departments for information about foot and ankle injuries related to high-heeled shoes over a 10-year period.¹ They estimated that more than 123,000 high-heel-related injuries were recorded in the United States during that time span. The age group at highest risk was women 20 to 29 years old. The most common injuries were to the feet and ankles (72%), usually sprains or strains. The vast majority of injuries (98.7%) were “nonsevere.” Surprisingly to me, half of all high-heel-related injuries happened at home (with another 33% occurring on some other property and 10% on the “street or highway”).

The authors concluded that people should be “conscious of” their footwear when at home and generally “reduce the time of exposure” to high-heeled shoes.

That advice is uncommonly bland, even by medical standards. But I understand why they tippy-toed around their own recommendations. I certainly would never want anyone telling *me* that some of my beloved shoes just need to go.



JON O. NEHER, MD

REFERENCE

- Moore JX, Lambert B, Jerkins GP, McGwin G Jr. Epidemiology of high-heel shoe injuries in U.S. women: 2002 to 2012. *J Foot Ankle Surg.* 2015; 54(4):615–619.

EDITOR-IN-CHIEF

Jon Neher, MD, FAAFP
Renton, WA

FOUNDING EDITOR-IN-CHIEF

Bernard Ewigman, MD, MSPH, FAAFP
Chicago, IL

EDITORIAL BOARD

Roselyn Jan W. Clemente-Fuentes, MD, FAAFP
Eglin, FL

Linda Montgomery, MD
Denver, CO

John E. Delzell, Jr., MD, MSPH
Miramar, FL

Mark B. Stephens, MD, MS, FAAFP
State College, PA

Philip Dooley, MD, FAAFP
Wichita, KS

Timothy Mott, MD, FAAFP
Executive Editor
Pensacola, FL

Scott Grogan, DO, MBA, FAAFP
Tacoma, WA

LuShawna Romeo
Executive Director
Columbia, MO

Alma Littles, MD
Tallahassee, FL

Douglas Maurer, DO, MPH, FAAFP
Tacoma, WA

EDITORS

HelpDesk Answers

Diving for PURLs

Tom Satre, MD
St. Cloud, MN

Corey Lyon, DO
Denver, CO

SECTION EDITORS

Behavioral Health Matters
Vanessa Rollins, PhD
Denver, CO

Geriatrics
Irene Hamrick, MD
Madison, WI

Musculoskeletal Health
Andrew W. Gottschalk, MD
Cleveland, OH

EBM on the Wards
Corey Lyon, DO
Denver, CO

Integrative Medicine
Adam Rindfleisch, MD
Madison, WI

Pharmacy HDAs
Connie Kraus, PharmD, BCACP
Madison, WI

EBPediatrics
Jonas A. Lee, MD
A. Ildiko Martonffy, MD
Madison, WI

Maternity Care
Lee Dresang, MD
Madison, WI

PRODUCTION

Medical Copy Editor
Melissa L. Bogen, ELS
Greenwood Lake, NY

Managing Editor
Adelina Colbert, BSc
Columbia, MO

Editorial Assistant
Abigail Beeler, BS
Columbia, MO

Design
Robert Thatcher
Haworth, NJ

STATEMENT OF PURPOSE

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

EDITORIAL POLICY

Statements and opinions expressed in articles and communications in this journal are those of the author(s) and not necessarily those of the editor, publisher, or any organizations endorsing this journal. The Publisher and editors of EBP do not endorse any methods, products, or ideas mentioned in the journal, and disclaim any liability which may arise from any material herein. Unless noted, authors have reported no competing interests and have nothing to disclose.

DISCLOSURE

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

2017 SUBSCRIPTION RATES

PERSONAL SUBSCRIPTIONS:	
FPIN Member	\$59
Non-member	\$119
International (outside of the US or Canada)	\$179
INSTITUTIONAL SUBSCRIPTIONS:	
US and Canadian Institutions	\$209
International Institutions	\$259
EBP Electronic Archives	\$500

Third Class postage paid at Columbia, MO 65202.

The GST number for Canadian subscribers is 124002536.

Postmaster: Send address changes to FPIN, Inc., 401 West Boulevard North, Suite D, Columbia, MO 65203; Attn: Adelina Colbert. Adelina@fpin.org. 573-256-2066.

Copyright © 2017 by Family Physicians Inquiries Network, Inc.

Should adult patients undergoing cardiac surgery receive preoperative statin therapy?

EVIDENCE-BASED ANSWER

In adult patients undergoing coronary artery bypass grafting (CABG), preoperative statin therapy reduces the incidence of postoperative atrial fibrillation (AF) by 50% and length of hospital stay by about a half day, but does not reduce short-term mortality. No benefit is seen with preoperative statin therapy for isolated valvular surgery in the absence of other indications for statin therapy (SOR: **A**, systematic reviews). Patients scheduled for CABG should receive at least 1 week of statin therapy; those undergoing emergency CABG should receive high-potency statin therapy (SOR: **C**, expert opinion).

Evidence summary

A 2015 systematic review examined 17 RCTs including 2,138 adult patients undergoing on- or off-pump cardiac surgery.¹ The reviewers compared the effectiveness of preoperative statin therapy against no statin therapy (or placebo) for reducing major adverse cardiovascular events. Sixteen studies reported the duration of preoperative statin therapy, which varied from immediately before surgery to 4 weeks (median 7 days). In 13 RCTs (n=1,686) participants underwent CABG exclusively; 4 studies (n=452) included patients who had combined procedures including aortic valve surgery.

Statin therapy did not influence the primary outcome, short-term mortality (2 trials, n=1,137; odds ratio [OR] 1.8; 95% CI, 0.38–8.5); however, analysis of secondary outcomes showed statin therapy reduced the incidence of postoperative AF (12 studies, n=1,765; OR 0.54; 95% CI, 0.43–0.67), time in the intensive care unit (ICU) (9 studies, n=721; weighted mean difference [WMD] –3.19 hours; 95% CI, –5.41 to –0.98), and hospital length of stay (11 studies, n=1,137; WMD –0.48 days; 95% CI, –0.78 to –0.19). Statin therapy did not influence postoperative stroke, myocardial infarction, or renal failure. No perioperative adverse effects of statins were identified.¹

A 2016 meta-analysis of 12 RCTs including 1,116 statin-naïve adult patients examined postoperative AF, hospital length of stay, and C-reactive protein (CRP) levels in patients treated with a statin versus placebo or no statin.² Eleven of

the 12 RCTs examined patients undergoing CABG or CABG plus valvular surgery, and 10 RCTs were included in the 2015 systematic review above.

Statin therapy was associated with a decrease in incidence of postoperative AF (12 studies, n=1,116; RR 0.50; 95% CI, 0.41–0.61), hospital length of stay (9 studies, n=972; mean difference –0.44 days; 95% CI, –0.67 to –0.2), and postoperative CRP level (7 studies, n=867; mean difference –12.4 mg/L; 95% CI, –23.9 to –0.87). No significant difference was found in ICU length of stay (7 studies, n=522; mean difference –0.47 hours; 95% CI, –2.2 to 1.0).²

In 2011, the American College of Cardiology (ACC) Foundation and American Heart Association (AHA) Task Force on Practice Guidelines concluded that it is reasonable to treat patients undergoing CABG with statin therapy, unless contraindicated, beginning ≥ 1 week before surgery (AHA/ACC class 1, level of evidence A: treatment should be administered, based on data derived from multiple RCTs).³ The Task Force also concluded it is reasonable to initiate high-dose statin therapy in patients undergoing urgent or emergent CABG (AHA/ACC class 2a, level of evidence C: it is reasonable to administer treatment, based on expert opinion).

In their 2014 practice guidelines on management of patients with valvular disease, the AHA/ACC Task Force did not comment on preoperative statin therapy for the management of patients with valvular heart disease.⁴ **EBP**

TARA SIMPSON, MD
LYNN OLIVER, MD
CHRISTINA TANNER, MD
 UWFM
 SEATTLE, WA

REFERENCES

1. Kuhn EW, Slottosch I. Preoperative statin therapy for patients undergoing cardiac surgery. *Cochrane Database Syst Rev*. 2015; (8):CD008493. [STEP 1]
2. Rezaei Y, Gholami-Fesharaki M, Dehghani MR, Arya A, Haghjoo M, Arjmand N. Statin antiarrhythmic effect on atrial fibrillation in statin-naïve patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. *J Cardiovasc Pharmacol Ther*. 2016; 21(2):167–176. [STEP 1]
3. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2011; 58(24):e123–e210. [STEP 1]
4. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014; 63(22):e57–e185. [STEP 1]

Got A-fib? Just DOAC it!

Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ*. 2016; 353:i3189.

This large cohort study from 3 nationwide Danish databases examined the effectiveness of 3 direct oral anticoagulants (DOACs) compared with warfarin in 61,678 patients with atrial fibrillation. Patients were newly diagnosed atrial fibrillation (excluded valvular disease or venous thromboembolism) and were prescribed standard dosing of DOACs (dabigatran 150 BID, rivaroxaban 20 mg daily, apixaban 5 mg BID) or warfarin. Patients were followed for an average of 1.9 years.

No differences in ischemic stroke or systemic emboli were seen among the 4 treatments (2.9–3.9 events per 100 person-years for DOACs vs 3.3 events per 100 person-years for warfarin; no *P* values provided). Ischemic stroke or systemic emboli events were less frequent in the rivaroxaban group compared with warfarin at 1 year (hazard ratio [HR] 0.83; 95% CI, 0.69–0.99); apixaban and dabigatran were no different from warfarin at 1 year.

Bleeding events (defined as intracranial, major gastrointestinal, and traumatic intracranial) were lower in the apixaban group (HR 0.63; 95% CI, 0.53–0.76) and dabigatran group (HR 0.61; 95% CI, 0.51–0.74) compared with warfarin. No difference was noted in bleeding events between the rivaroxaban and warfarin groups.

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

Bottom line: In patients with newly diagnosed atrial fibrillation, all direct oral anticoagulants are just as effective for preventing ischemic stroke and systemic emboli as warfarin. Rivaroxaban is possibly more effective than warfarin (with equal bleeding rates). Apixaban and dabigatran are equally effective as warfarin and have lower bleeding rates.

REVIEW AUTHOR: ALEX REED, PSYD, MPH,
UNIVERSITY OF COLORADO FMR, AURORA, CO

SUMMARY AUTHORS: ALEX REED, PSYD, MPH,
AND COREY LYON, DO, UNIVERSITY OF COLORADO FMR, AURORA, CO

Exercise and arthroscopy provide similar outcomes for medial meniscal tears

Kise NJ, Risberg MA, Stensrud S, Ranstam J, Engebretsen L, Roos EM. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. *BMJ*. 2016; 354:i3740.

This RCT compared exercise therapy with arthroscopic partial meniscectomy in patients 35 to 60 years old who had unilateral knee pain for >2 months and a MRI-delineated medial meniscal tear presenting to orthopedics in Norway. Patients were randomized to 12 weeks (24–36 sessions) of exercise therapy or a standardized arthroscopic partial meniscectomy with written and oral encouragement to perform simple home exercise 2 to 4 times daily.

The primary outcomes were patient-reported overall knee osteoarthritis outcome score (KOOS) after 2 years and 3-month thigh muscle strength. The KOOS consists of 5 subscales (pain, symptoms, function in sports/recreation, knee-related quality of life [QOL], and activities of daily living [ADL]), in which each subscale is scaled from 0 (worst) to 100 (best). Secondary outcomes included individual KOOS subscales and objective lower extremity strength testing.

The overall mean improvement in KOOS score from baseline at 2 years was similar in the exercise and meniscectomy groups (25 vs 24 points; mean difference [MD] 0.9; 95% CI, –4.3 to 6.1). Secondary outcomes comparing the change from baseline of the KOOS subscales showed 4 of the 5 subscales had nonsignificant differences (pain, function in sports/recreation, QOL, and ADL). Only the symptoms subscale had a slightly significant difference favoring exercise therapy (MD 5.3; 95% CI, 0.5–10). Additionally, muscle strength testing at both 3 and 12 months found significant improvements favoring exercise therapy.

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

Bottom line: For middle-aged patients with minimal underlying osteoarthritis who have a medial meniscal tear, exercise therapy is as effective as surgery with potential benefits in muscle strength.

REVIEW AND SUMMARY AUTHORS: SANDY SAUERESIEU, MD, MPH,
UPMC ST. MARGARET FMRP, PITTSBURGH, PA, AND JENNIE B. JARRETT,
PHARMD, BCPS, MMEDED, UNIVERSITY OF ILLINOIS AT CHICAGO

Shorter courses for CAP antibiotics

Uranga A, España PP, Bilbao A, Quintana JM, Arriaga I, Intxausti M, et al. Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. *JAMA Intern Med.* 2016; 176(9):1257–1265.

This double-blind, randomized trial compared short-term antibiotic treatment duration with physician-discretion treatment duration among 312 patients aged ≥ 18 years admitted for community-acquired pneumonia (CAP). After receiving a minimum of 5 days of antibiotics, patients were randomized either to an intervention group, in which if they were clinically stable, no further antibiotics were given, or to a control group, in which physicians determined antibiotic duration.

Primary outcomes for the study were clinical success rates at days 10 and 30 since admission, defined as resolution of signs and symptoms of CAP and improvement of CAP-related symptoms via a patient questionnaire. Secondary outcomes included duration of antibiotic use, time to clinical improvement, mortality, hospital readmissions, and length of stay, among others.

For antibiotic selection, nearly 80% of patients received quinolone treatment and less than 10% of patients received beta-lactam antibiotic treatment. The primary outcome of clinical success rates in the intent-to-treat (ITT) analysis were similar at day 10 in the control group and intervention group (49% vs 56%; $P=.18$) and at 30 days (89% vs 92%; $P=.33$). Secondary outcomes with statistical differences included a shorter median treatment duration for antibiotics in the intervention group compared with control (5 vs 10 days; $P<.001$) and fewer 30-day readmissions (1.4% vs 6.6%; $P=.02$). No other statistical differences in secondary outcomes were identified.

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

Bottom line: Five days of antibiotic treatment for CAP appears to be as effective as longer therapy for clinical success rates without yielding any worsening patient outcomes, particularly with quinolone treatments.

REVIEW AND SUMMARY AUTHORS: GREGORY CASTELLI, PHARM.D, BCPS, BC-ADM, UPMC ST. MARGARET FMHP, PITTSBURGH, PA, AND JENNIE B. JARRETT, PHARM.D, BCPS, MMEDED, UNIVERSITY OF ILLINOIS AT CHICAGO

Which is the safest combined oral contraceptive pill?

Weill A, Dalichamp M, Raguideau F, Ricordeau P, Blotière PO, Rudant J, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. *BMJ.* 2016; 353:i2002.

This observational cohort study included almost 5 million patients, mean age 28 years, using combination oral contraceptives to assess the risk of adverse cardiovascular outcomes over 2 years. The combined oral contraceptives contained varying doses of ethinyl estradiol (20–50 μg) and different progestogens. Outcomes measured included the risk of pulmonary embolism (PE), myocardial infarction (MI), and ischemic stroke for different combinations of estrogen dose with the same progesterone, and for different progestogens.

After adjusting for type of progestogen, socioeconomic status, age, diabetes, hypertension, and tobacco use, women using low-dose (20 μg) versus higher dose estrogen (30–40 μg) had a lower risk of PE (risk ratio [RR] 0.75; 95% CI, 0.67–0.85), ischemic stroke (RR 0.82; 95% CI, 0.70–0.96), and MI (RR 0.56; 95% CI, 0.39–0.79). After adjusting for type of estrogen and risk factors, compared with levonorgestrel, the progestogens gestodene (RR 1.6; 95% CI, 1.34–1.97) and desogestrel (RR 2.2; 95% CI, 1.93–2.41) had a higher risk of PE. Study limitations included short duration, unknown length of contraception use, and unknown confounders.

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

Bottom line: Oral contraceptives containing low-dose estrogen (20 μg) combined with levonorgestrel, compared with pills containing higher dose estrogen or the progestins gestodene and desogestrel, have the lowest risk of PE. **EBP**

REVIEW AUTHOR: YEE LAM, MD, PHD, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL, CHAPEL HILL, NC

SUMMARY AUTHOR: ANNE MOUNSEY, MD, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL, CHAPEL HILL, NC

Additional information regarding the PURLs and Diving for PURLs series can be found at: <http://www.fpin.org/purls-faqs/>

Should you treat a subsegmental pulmonary embolism (PE) with anticoagulation?

CASE

A 73-year-old man with a history of tobacco abuse was admitted for a fall and altered mental status. Further history revealed a recent unexplained 30-pound weight loss. The patient denied cough, chest pain, shortness of breath, or leg swelling. Vital signs showed a blood pressure of 143/87 mmHg, heart rate of 81 bpm, and an oxygen saturation of 96% on room air. A contrast-enhanced computed tomography (CT) scan of his chest, abdomen, and pelvis for evaluation revealed a left lower lobe subsegmental pulmonary artery filling defect. Should this patient with an incidental subsegmental pulmonary embolism (SSPE) be treated with anticoagulation?

Review of the evidence

A 2010 retrospective analysis identified a cohort of 93 patients with isolated SSPE on computed tomographic pulmonary angiography (CTPA) and compared clinical outcomes (hemorrhage, venous thromboembolism [VTE] recurrence, death) of patients who were observed versus treated over a 3-month period.¹

Of the 22 (24%) patients who were observed, none hemorrhaged, had recurrent VTE, or died. Of the 71 (76%) patients who were treated with anticoagulation and/or inferior vena cava filter, 1 patient had a recurrent SSPE (1.0%) and 8 patients had bleeding events (8.5%), 5 of which were major hemorrhages. The authors concluded that isolated untreated SSPE have favorable 3-month outcomes.¹

A 2010 systematic review of 20 prospective cohort studies and 2 RCTs evaluated diagnosis and outcomes of patients with suspected PE who underwent single-detector (n=1,123) and multiple-detector CTPA (n=1,534).²

The rate of SSPE diagnosis was 4.7% (95% CI, 2.5–7.6) in patients who underwent single-detector CTPA and 9.4% (95% CI, 5.5–14) in patients who underwent multiple-detector CTPA. The 3-month risk of symptomatic VTE in untreated patients with suspected PE and a negative CTPA was 0.9% (95% CI, 0.4–1.4) for single-detector CTPA and 1.0% (95% CI, 0.7–1.4) for multiple-detector CTPA (no *P* value provided). The authors suggested SSPEs may not be clinically relevant because multiple-detector CTPA increased the proportion of

patients diagnosed with SSPE without lowering the 3-month risk of VTE.²

The 2016 evidence-based *Chest* guideline reported no episodes of recurrent VTE in retrospective studies that included about 60 patients with SSPE and no proximal deep vein thrombosis (DVT) who did not undergo anticoagulation.³ They recommended clinical surveillance over anticoagulation in patients with SSPE, no proximal DVT in the lower extremities, and low risk for recurrent VTE (Grade 2C, weak recommendation based on low-quality evidence).

CASE WRAP-UP

Our patient underwent ultrasound of his lower extremities, which did not show any developing DVT. We opted to observe him without therapy. Three months after discharge, he was doing well with no evidence of recurrent VTE.

EBP

HARRIET HUANG, MD

COREY LYON, DO

UNIVERSITY OF COLORADO FMR
DENVER, CO

REFERENCES

1. Donato AA, Khoche S, Santora J, Wagner B. Clinical outcomes in patients with isolated subsegmental pulmonary emboli diagnosed by multidetector CT pulmonary angiography. *Thromb Res*. 2010; 126(4):e266–e270. [STEP 3]
2. Carrier M, Righini M, Wells PS, Perrier A, Anderson DR, Rodger MA, et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. *J Thromb Haemost*. 2010; 8(8):1716–1722. [STEP 3]
3. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: Chest guideline and expert panel report. *Chest*. 2016; 149(2):315–352. [STEP 1]

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.

Is hyaluronic acid more effective than corticosteroids for the treatment of osteoarthritis (OA) of the knee?

EVIDENCE-BASED ANSWER

Perhaps. There is no difference between intra-articular hyaluronic acid (IAHA) and intra-articular steroids (IAS) for reducing pain from knee OA 1 to 4 weeks postinjection. At later postinjection time points (5–13 weeks and 13–26 weeks), IAHA has a 15% higher response rate than IAS and is modestly more effective than IAS in improving function, with inconsistent effects on pain. There appear to be no significant differences in adverse events between IAS and IAHA (SOR: **B**, 2 meta-analyses with divergent results).

A 2016 network meta-analysis of 11 RCTs (N=3,391) evaluated the relative efficacies of IAS versus placebo, IAHA versus placebo, or IAS versus IAHA in patients with knee OA.¹ The English-language studies reported outcomes using the Western Ontario and McMaster University Arthritis Index (WOMAC) evaluating mean change in baseline of pain, stiffness, and function.

The WOMAC index consists of 3 categories, which include pain (5 items), stiffness (2 items), and physical function (17 items) measured on a Likert scale (score 0–5) or a 100-mm visual analog scale (VAS) (higher numbers represent worse symptoms). A response was defined as either an improvement in WOMAC pain or function of 50% or more and absolute change of 20 mm or more on the VAS, or 2 of the following 3 possibilities: at least 20% improvement in pain and at least a 10-mm VAS absolute change; at least 20% improvement in function and at least a 10-mm VAS absolute change; or at least 20% improvement in patient’s global assessment and at least a 10-mm VAS absolute change.¹

Treatment protocols varied by study and included Hyalgan, Hylastan, or bioHA versus saline placebo or triamcinolone hexacetonide; the number of weekly injections varied from 1 to 5. Time points studied included 13 to 26 weeks postinjection.¹

Patients who received IAHA were 15% more likely to respond than patients who received IAS (2 trials, n=not reported; relative risk [RR] 1.15; 95% CI, 1.02–1.30) and 11%

more likely to respond than patients who received placebo (4 trials, n=not reported; RR 1.11; 95% CI, 1.01–1.20). Response with IAS was not different from placebo. IAHA improved the WOMAC function score to a small degree compared with IAS (2 trials, n=not reported; effect size –0.29; 95% CI, –0.53 to –0.05) but not pain or stiffness scores. Most studies did not show a significant difference in adverse events; however, in 1 study (n=442) there was a 17.2% incidence in arthralgia with IAHA (which resolved within 2–3 weeks) compared to 3.2% with IAS ($P<.01$).¹

A 2009 systematic review of 28 RCTs (N=1,973) evaluated the efficacy and safety of IAS for treatment of knee OA.² Only 1 study is in common with the meta-analysis above. Inclusion criteria included diagnosis of OA, RCT, specification of comparative treatment, and published data on relevant outcome measures. Studies included IAS versus placebo, IAHA products, joint lavage, and other IA corticosteroids. The primary outcome was efficacy and safety of IAS, with efficacy being defined as reduction in knee pain as measured on the 100-mm VAS.

Three studies (n=170) compared methylprednisolone and Hyalgan (dose and number of injections not specified) and demonstrated no significant difference in pain reduction on VAS between Hyalgan and methylprednisolone at 1 to 4 weeks postinjection (weighted mean difference [WMD] –4.9; 95% CI, –9.9 to 0.1). At 5 to 13 weeks postinjection, however, Hyalgan was more effective than methylprednisolone (WMD –7.7; 95% CI, –12.8 to –2.6). One parallel-group, single-blinded RCT (n=218) comparing 3 weekly injections of hylan G-F 20 with 1 injection of triamcinolone hexacetonide demonstrated that hylan G-F 20 improved function on the WOMAC more than triamcinolone between 5 and 13 weeks (WMD –5.0; 95% CI, –8.9 to –1.14) and 14 and 26 weeks (WMD –5.2; 95% CI, –9.1 to –1.3). No significant safety differences or adverse events were reported.²

ANGELENE ELLIOTT, DO
HARRY COLT, MD
 MAINE DARTMOUTH FMR
 AUGUSTA, ME

1. Trojian TH, Concoff AL, Joy SM, Hatzenbuehler JR, Saulsberry WJ, Coleman CI. AMSSM scientific statement concerning viscosupplementation injections for knee osteoarthritis: importance for individual patient outcomes. *Clin J Sport Med.* 2016; 26(1):1–11. [STEP 1]
2. Bellamy N, Campbell J, Welch V, Gee TL, Bourne R, Wells GA. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev.* 2009; (2):CD005328. [STEP 1]

Is image-guided glucocorticoid injection superior to landmark-based glucocorticoid injections for shoulder pain?

EVIDENCE-BASED ANSWER

Not by much. While image-guided injection may improve shoulder range of motion (ROM), data are conflicting regarding pain and it does not improve function when compared to landmark-based injection for shoulder pain (SOR: **B**, systematic reviews of heterogeneous randomized and nonrandomized trials).

A 2012 systematic review of 3 RCTs and 2 controlled clinical trials (N=290) compared image-guided (ultrasound, arthrogram, MRI) shoulder injection with landmark-based injection in patients with shoulder pain secondary to adhesive capsulitis or rotator cuff disease.¹ The study included all randomized and quasirandomized trials. The primary outcomes included overall pain and function scores. Pain was measured by either visual analog scale or numerical or categorical rating scales. Function was assessed with the Shoulder Pain and Disability Index (SPADI) or Constant score.

Pain was significantly reduced at 6 weeks in the image-guided injection group compared with the landmark-based group (3 trials, n=207; standardized mean difference [SMD] -0.80; 95% CI, -1.5 to -0.14). However, when the 4 studies with inadequate allocation concealment or inadequate participant blinding were excluded, the remaining study shows no difference in pain reduction at 1 to 2 weeks or 6 weeks postinjection. No difference was noted between groups in measures of function at 1 to 2 weeks, or 6 weeks postinjection. The authors concluded that ultrasound-guidance may increase the accuracy of needle placement into the area of pathology, but did not improve outcomes over landmark-based injections.¹

A 2013 systematic review of 2 randomized and 4 nonrandomized controlled trials (N=307) compared ultrasound-guided and landmark-based shoulder injections for pain relief, ROM, and night pain at 6 weeks postinjection.² Patients ranged in age from 52 to 58 years and had a variety of shoulder injuries, including subacromial bursitis, rotator cuff impingement, and adhesive capsulitis. Studies used different methods to assess pain scores.

Ultrasound-guided injection resulted in improved pain (3 studies, n=164; SMD 1.0; 95% CI, 0.12–1.9), abduction ROM (2 studies, n=100; mean difference [MD] 2.8 degrees; 95% CI, 0.67–5.0), and night pain (SMD 0.4; 95% CI, 0.02–0.79) compared with landmark-based injections. The study authors, however, stated the magnitudes of the differences might not be clinically meaningful.²

JOHN OLSHEFSKI, MD

SCOTT WILTZ, MD

EGLIN AIR FORCE BASE

EGLIN, FL

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.

1. Bloom JE, Rischin A, Johnston RV, Buchbinder R. Image-guided versus blind glucocorticoid injection for shoulder pain. *Cochrane Database Syst Rev.* 2012; (8):CD009147. [STEP 2]
2. Sage W, Pickup L, Smith TO, Denton ER, Toms AP. The clinical and functional outcomes of ultrasound-guided vs landmark-guided injections for adults with shoulder pathology—a systematic and meta-analysis. *Rheumatology (Oxford).* 2013; 52(4):743–751. [STEP 2]

Does ImPACT testing provide an accurate neurocognitive baseline for athletes with learning disabilities?

EVIDENCE-BASED ANSWER

At baseline, athletes with self-reported learning disabilities (LD) or attention-deficit/hyperactivity disorder (ADHD) demonstrate decreased performance in immediate postconcussion assessment and cognitive testing (ImPACT), including verbal and visual memory, visual motor speed, reaction time, and symptom score compared with unaffected athletes (SOR: **C**, cohort and case-control studies of disease-oriented outcomes).

ImPACT is a widely used, computerized tool for managing concussions in athletes.

A 2013 matched cohort study compared baseline ImPACT test results for concussion evaluation among high school athletes with LD, ADHD, both conditions, or neither condition (N=814).¹ ImPACT composite scores for 6 areas (verbal memory, visual memory, visual motor speed, reaction time, impulse control, total symptoms) were compared among 4 different groups (control, self-reported

TABLE 1

Mean baseline ImPACT composite scores for athletes with LD, ADHD, and controls¹

ImPACT score (99th percentile score) ^a	LD only ^b (n=90)	ADHD only ^b (n=262)	LD & ADHD ^b (n=55)	Control (n=407)
Verbal memory (100)	79	79	80	84
Visual memory (97)	69	70	68	75
Visual motor speed (52)	32	35	33	37
Reaction time (0.36)	0.64	0.63	0.65	0.60
Impulse control ^c	7.3	7.7	7.0	6.4
Total symptom score ^d	7.9	8.1	9.4	3.7

ADHD=attention-deficit hyperactivity disorder; ImPACT=immediate postconcussion assessment and cognitive testing; LD=learning disability.

^aThe 99th percentiles for 16- to 18-year-old males from impacttest.com are provided for reference; scores are without units, calculated based on number of correct responses.

^b $P < .001$ vs controls.

^cSum of errors committed during the test.

^dAthletes reported 22 symptoms on a scale of 1 (mild) to 6 (severe); thus, 4 symptoms with a severity of 3 would score a total of 12.

TABLE 2

Mean baseline ImPACT composite scores for athletes with LD, ADHD, and controls²

ImPACT score (99th percentile score) ^a	LD only ^b (n=396)	ADHD only ^b (n=882)	LD & ADHD ^b (n=161)	Control (n=938)
Verbal memory (100)	82	83	81	84
Visual memory (97)	68	69	68	72
Visual motor (52)	32	36	33	37
Reaction time (0.36)	0.63	0.60	0.63	0.59
Symptom score ^c	4.0	4.5	4.5	3.1

ADHD=attention-deficit hyperactivity disorder; ImPACT=immediate postconcussion assessment and cognitive testing; LD=learning disability.

^aThe 99th percentiles for 16- to 18-year-old males from impacttest.com are provided for reference; scores are without units, calculated based on number of correct responses.

^b $P = .001$ ANCOVA among the 4 groups.

^cAthletes reported 22 symptoms on a scale of 1 (mild) to 6 (severe); thus, 4 symptoms with a severity of 3 would score a total of 12.

LD-only, self-reported ADHD-only, self-reported LD/ADHD) (see **TABLE 1**).

Athletes with LD were found to have a statistically significant decrease in scoring in all areas, except impulse control. Athletes with ADHD-only had statistically significant differences in all 6 domains. Athletes with LD and ADHD demonstrated statistically significant differences in visual motor speed, reaction time, and total symptom score. Limitations of this study included potential biases in recall, selection, self-reporting of diagnoses, inability to control for medication usage, and variable testing environments.¹

A 2013 retrospective cross-sectional study investigated whether preparatory and collegiate athletes with a self-reported diagnosis of LD and/or ADHD had lower baseline ImPACT results than controls (N=2,377, averaging 15 years old, 63% males) among participants with ImPACT results obtained between 2009 and 2011 (see **TABLE 2**).²

The control group had higher performance in all areas tested. The analysis of means using ANCOVA found statistically significant differences ($P = .001$) among the 4 groups on each of the 5 scores. Study limitations included lack of control for testing conditions, self-reporting of diagnoses, inability to

account for medication effects, and lack of consideration for diagnosis subtypes.²

JOHN K. DANIELS, MD
SCHOOL OF MEDICINE UNIVERSITY OF NEVADA
RENO, NV

1. Zuckerman SL, Lee YM, Odom MJ, et al. Baseline neurocognitive scores in athletes with attention deficit-spectrum disorders and/or learning disability. *J Neurosurg Pediatr.* 2013; 12(2):103–109. [STEP 3]
2. Elbin RJ, Kontos AP, Kegel N, et al. Individual and combined effects of LD and ADHD on computerized neurocognitive concussion test performance: evidence for separate norms. *Arch Clin Neuropsychol.* 2013; 28(5):476–484. [STEP 3]

What is the best treatment for *Giardia*?

EVIDENCE-BASED ANSWER

The 5-nitroimidazole (5-NI) class of antimicrobials, including metronidazole and tinidazole, are 10% to 30% more likely to result in cure than other antiparasitic agents for *Giardia* in adults and children (SOR: **A**, meta-analysis of RCTs). Single-dose tinidazole is 40% to 90% more likely to result in cure than albendazole for eradication of *Giardia* in children (SOR: **A**, meta-analysis of RCTs).

A 2014 meta-analysis of 30 RCTs (N=3,930) compared the efficacy of 5-NIs (metronidazole, tinidazole, secnidazole, and ornidazole) with other therapies for the treatment of giardiasis in adults and children.¹ Of the included RCTs, 22 exclusively studied children, 2 exclusively studied adults, and 4 included both. Other treatments included quinacrine, furazolidone, albendazole, mebendazole, paromomycin, bacitracin zinc, chloroquine, and nitazoxanide. Doses of medications varied across studies.

The primary outcome was parasitological cure at 3 days to 5 weeks. Adverse outcomes evaluated included abdominal pain, metallic or bitter taste, and headache.¹

The 5-NIs demonstrated a slightly higher parasitological cure compared with the other treatments (25 trials, n=3,677; relative risk [RR] 1.1; 95% CI, 1.0–1.1). A subgroup analysis of the 2 5-NIs available in the United States demonstrated similar superior efficacy (metronidazole: 18 trials, n=2,196; RR 1.1; 95% CI, 1.0–1.1; and tinidazole: 4 trials, n=592; RR 1.3; 95% CI, 1.1–1.6). Overall, the 5-NIs were associated with less abdominal pain (24 trials, n=3,215; RR 0.72; 95% CI, 0.57–0.91),

but higher rates of metallic taste and headache than the other treatments (22 trials, n=2,979; RR 3.3; 95% CI, 2.7–4.0 and 23 trials, n=3,018; RR 2.0; 95% CI, 1.4–2.8, respectively).¹

A 2016 meta-analysis of 5 RCTs (N=403) compared tinidazole administered as a single 50-mg/kg dose with albendazole administered in doses ranging from a single 800-mg dose to 400 mg daily for 5 days for the treatment of *Giardia* infections in children.² The primary outcome was parasitological cure (negative *Giardia* in fecal specimens) within 21 days after treatment.

Tinidazole was superior in parasitological cure compared with albendazole (5 trials, n=423; RR 1.6; 95% CI, 1.4–1.9; number needed to treat=4). Tinidazole was associated with greater compliance and less adverse events than albendazole (data not provided). This meta-analysis included children in Peru, Thailand, and Cuba.²

ELIZABETH HESS, MD
BRENT McMILLION, MD
JOANNE NIERE, MD
UNITED HOSPITAL CENTER FAMILY MEDICINE
BRIDGEPORT, WV

1. Pasupuleti V, Escobedo AA, Deshpande A, Thota P, Roman Y, Hernandez AV. Efficacy of 5-nitroimidazoles for the treatment of giardiasis: a systematic review of randomized controlled trials. *PLoS Negl Trop Dis.* 2014; 8(3):e2733. [STEP 1]
2. Escobedo AA, Ballesteros J, González-Fraile E, Almirall P. A meta-analysis of the efficacy of albendazole compared with tinidazole as treatments for *Giardia* infections in children. *Acta Trop.* 2016; 153:120–127. [STEP 1]

In pregnant women, does use of hair dye increase rates of adverse fetal outcomes?

EVIDENCE-BASED ANSWER

Use of hair dye during pregnancy is associated with a 60% increased risk of neuroblastoma, but no increased risk of malignant primary brain tumors or cranial nerve and meningeal tumors (SOR: **C**, case-control studies).

A 2005 case-control study evaluated the risk of neuroblastoma occurring in children with mothers who used hair dye 1 month before a positive pregnancy test or throughout pregnancy.¹ Cases of newly diagnosed neuroblastoma in children younger than 19 years were obtained from a large cancer database from 139 hospitals in the United States and Canada. Controls were matched

to a case patient based on age and telephone number area code.

Trained interviewers collected data on type, timing, and frequency of hair dye and risk factors for neuroblastoma (family medical history; medication and vitamin use; and occupational, household, and lifestyle exposures) from the mothers of the case and control patients by telephone. Permanent hair dye was defined as “does not wash out and leaves a line as the hair grows” and temporary hair dye defined as “washes out after one or several shampoos.” Only completed phone interviews were used in the final analysis and were obtained for 538 of 741 identified cases (73%) and 504 of 703 matched controls (72%). The incidence of hair dye exposure was 23% (124 of 538) in case patients and 16% (81 of 504) in control patients.¹

Any hair dye exposure had a statistically significant increase in the risk of neuroblastoma (odds ratio [OR] 1.6; 95% CI, 1.2–2.2). A statistically significant increase in neuroblastoma rates occurred with temporary hair dye use (OR 2.0; 95% CI 1.1–3.7), but not with permanent hair dye use (OR 1.4; 95% CI, 1.0–2.0) or hair dye use during the 1 month before pregnancy (OR 1.4; 95% CI, 0.9–2.2).¹

A 2002 case-control study also evaluated the risk of childhood brain tumors with mothers who used hair dye 1 month before a positive pregnancy test or throughout pregnancy.² Cases were identified from population-based cancer registries of Los Angeles County, 5 counties in the San Francisco Bay area, and 13 counties in the Seattle-Puget Sound area. Cases included children younger than 20 years at diagnosis with benign or malignant primary brain tumor, or cranial nerve/meninges tumor. Controls were matched to cases based on sex, birth year, and region.

The mothers of the case and control children were interviewed in person by a trained interviewer. Only completed interviews were used in the final analysis and were obtained for 540 of 762 identified cases (71%) and 801 of 1,079 matched controls (74%).²

The incidence of hair dye exposure was 12% (65 of 540) in case patients and 12% (96 of 801) in control patients. Hair dye use did not cause a statistically significant increase in the risk of childhood brain tumors (OR 0.96; 95% CI, 0.69–1.3). Possible confounding variables of prenatal vitamins, cured meat consumption, rubber nipple or pacifier use, new car exposure, and mother’s use of foundation make-up were included in a logistic model/regression

analysis, and also showed no differences in the risk of childhood brain tumors.²

NOUREEN ZOHRA, MD
JANICE FRUEH, PHARM D
 SIU SPRINGFIELD FMRP
 SPRINGFIELD, IL

1. McCall EE, Olshan AF, Daniels JL. Maternal hair dye use and risk of neuroblastoma in offspring. *Cancer Causes Control*. 2005; 16(6):743–748. [STEP 4]
2. Holly EA, Bracci PM, Hong MK, Mueller BA, Preston-Martin S. West Coast study of childhood brain tumors and maternal use of hair coloring products. *Paediatr Perinat Epidemiol*. 2002; 16(3):226–235. [STEP 4]

In patients with fibromyalgia, is low-dose naltrexone effective in alleviating pain, and does it decrease use of oral opioids?

EVIDENCE-BASED ANSWER

Used alone, low-dose naltrexone modestly reduces pain compared with placebo. No studies have addressed the effect of low-dose naltrexone on oral opioid use in patients with fibromyalgia (SOR: **B**, single small RCT and single nonrandomized pilot study).

A 2013 randomized, double-blind, placebo-controlled crossover study (N=31) compared naltrexone and placebo in patients with fibromyalgia.¹ The patients were all women aged 18 to 65 years who met the 1990 American College of Rheumatology (ACR) diagnostic criteria for fibromyalgia. Patients were excluded if they lived more than 2 hours from the laboratory, had any history or laboratory evidence of inflammatory or rheumatic disease, significant psychiatric distress, depression, or any concurrent opioid use.

After a 2-week period to establish their baseline pain level, patients were randomized to either 4 weeks of placebo or 12 weeks of naltrexone (4.5 mg/d) followed by crossover to the opposite arm without washout. An additional 4 weeks were added as follow-up. Pain self-assessment was recorded daily using the question “Overall, how severe has your pain been today?” on a 0 to 100 scale, with 0 defined as “no pain at all” and 100 as “the worst pain imaginable.” The average pain score from the entire 2-week baseline period was compared with the average pain score from the final 3 days before crossover or study termination.¹

CONTINUED

Naltrexone reduced pain more than placebo (29% vs 18%; $P=.016$). Vivid dreams and headache were the only 2 adverse events reported more frequently with naltrexone than placebo.¹

A 2009 single-blind, nonrandomized, crossover pilot study (N=10) compared placebo and low-dose naltrexone in patients with moderately severe fibromyalgia.² The patients were all women with an average age of 44 years who met the 1990 ACR diagnostic criteria for fibromyalgia. Patients were excluded for current opioid use, concurrent autoimmune or rheumatologic conditions, joint pain or inflammation, rheumatoid factor of more than 20 IU/mL, or erythrocyte sedimentation rate of more than 60 mm/h.

Each patient followed the same schedule: no treatment (baseline) for 2 weeks, placebo for 2 weeks, low-dose naltrexone (4.5 mg/d) for 8 weeks, and then washout for 2 weeks. Symptom severity was recorded daily using a 0 to 100 scale in response to the question, “Overall, how severe have your fibromyalgia symptoms been today?” Multiple secondary outcomes including tolerability and side effects were also recorded. The daily symptom log response rate was 92%.²

Naltrexone reduced symptoms compared with baseline by 33% ($P<.0005$), while placebo reduced symptoms compared with baseline by 2.3% ($P<.003$). Naltrexone was not directly compared with placebo. Six patients were considered naltrexone responders (30% reduction in symptoms) and 4 were considered nonresponders. Naltrexone daily tolerability was 96% versus 90% for placebo (significance not reported). Two patients reported vivid dreams with naltrexone and 1 reported nausea and insomnia.²

SHERYL BEARD, MD
LARY HILL, MD
 KUSM-W FMR AT VIA CHRISTI
 WICHITA, KS

1. Younger J, Noor N, McCue R, Mackey S. Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. *Arthritis Rheum.* 2013; 65(2):529–538. [STEP 2]
2. Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. *Pain Med.* 2009; 10(4):663–672. [STEP 3]

What are the cognitive risks associated with vitamin B₁₂ deficiency in the elderly?

EVIDENCE-BASED ANSWER

Whether serum vitamin B₁₂ levels in older adults are associated with cognitive changes is unclear. However, elevated levels of methylmalonic acid, a B₁₂ metabolite that reflects low vitamin B₁₂ function, are more consistently associated with cognitive decline (SOR: **B**, systematic reviews of longitudinal studies).

A 2013 systematic review, which included 4 longitudinal studies of 1,579 generally healthy elderly individuals, investigated whether an association existed between vitamin B₁₂ serum levels and cognitive function as measured by the Mini-Mental State Examination (MMSE) test.¹ The deviation of the MMSE score from the population mean was reported using z-scores and the regression coefficient was calculated to determine the relationship between the MMSE z-scores and vitamin B₁₂ levels. In the 3.3 to 9 years that the patients were studied, they completed an annual MMSE and their B₁₂ levels were measured.

No statistical association was found between the MMSE z-scores and B₁₂ serum levels ($\beta=0.00$, 95% CI, -0.00 to 0.01).¹

A 2012 systematic review of 35 longitudinal studies investigated the association of B₁₂ serum markers and cognition in 14,325 patients 47 to 85 years old from 10 countries with a mean follow-up of 5.4 years.² Inclusion criteria, such as level of initial cognition (if measured), degree of chronic disease, and amount of folate intake, differed substantially among the studies. Cognitive change was measured with different neuropsychological tests and outcomes were reported as cognitive decline, dementia, or Alzheimer’s dementia. Results could not be pooled for meta-analysis. Studies were defined as high quality if 3 reviewers agreed there was a low risk of bias based on the American Dietetic Association Study Quality criteria. Twenty-one of the initial 35 studies were defined as high quality.

Of the 21 high-quality studies, only 3 of 17 that used serum vitamin B₁₂ levels as the marker for B₁₂ status showed a significant association between low vitamin B₁₂ levels and cognitive decline. However, all 4 of the 21 high-quality studies that used methylmalonic acid as the serum marker of low

We invite your questions and feedback.
 Email us at EBP@fpin.org.

vitamin B₁₂ levels showed significant associations between cognitive decline and elevated methylmalonic acid. Individual results were not reported for most of the studies.²

ROBERT A. BECK, MD
CEDAR RAPIDS MEDICAL EDUCATION FOUNDATION
CEDAR RAPIDS, IA

1. Doets EL, van Wijngaarden JP, Szczecińska A, Dullemeijer C, Souverein OW, Dhonukshe-Rutten RA, et al. Vitamin B12 intake and status and cognitive function in elderly people. *Epidemiol Rev.* 2013; 35:2–21. [STEP 2]
2. O’Leary F, Allman-Farinelli M, Samman S. Vitamin B12 status, cognitive decline and dementia: a systematic review of prospective cohort studies. *Br J Nutr.* 2012; 108(11):1948–1961. [STEP 2]

In patients with uterine bleeding due to a progestin contraceptive implant, are combined oral contraceptives (COCs) helpful?

EVIDENCE-BASED ANSWER
Short-term (14–20 days) use of COCs reduces bleeding days and time to cessation of bleeding in implant users; however, bleeding reoccurs quickly after cessation of COC treatment (SOR: **B**, small RCTs). COCs are not recommended for routine treatment of irregular bleeding (SOR: **C**, expert opinion).

A 2013 systematic review of 33 RCTs addressed therapies for bleeding irregularities attributed to progestin-only contraceptives, including pill, injection, and implantable forms.¹ One trial specifically evaluated women (n=91), age not defined, with levonorgestrel implants (Norplant®) treated with a COC. Women presenting to clinic with more than 8 days of active bleeding were randomized to 20-day treatment with a COC containing levonorgestrel 250 µg plus ethinyl estradiol 50 µg or placebo, initiated on the day of presentation.

The COC resulted in 7% women having continued bleeding on day 20 compared with 85% taking placebo (relative risk of continued bleeding 0.08; 95% CI, 0.03–0.24). Mean total bleeding days during treatment was 2.6 in COC group versus 12.3 in the placebo group (mean difference [MD] –9.7; 95% CI, –11.3 to –8.1). Implant discontinuation due to bleeding was analyzed in 100 patients and was not significantly different between groups (0 of 50 in the COC group vs 1 of 50 in the placebo group). More than 10% of

participants dropped out, introducing potential bias. The authors did not recommend routine use of COC in medically eligible patients for the treatment of irregular bleeding because abnormal bleeding patterns resumed after COC treatment.¹

A 2015 RCT evaluated COCs in 32 women aged 18 to 44 with etonogestrel (Nexplanon®) progestin implants experiencing bothersome bleeding, defined as more than 7 continuous days of bleeding or spotting.² Women were randomized to a 14-day COC treatment with 150 µg levonorgestrel plus 30 µg ethinyl estradiol or placebo, initiated on the day of presentation.

COC treatment temporarily interrupted bleeding within 14 days in 88% of women in the COC group compared with 38% in the placebo group (odds ratio 11.7; 95% CI, 1.9–70.2). The median time to cessation of bleeding was shortened by 4 days in the COC group compared with placebo (median 5.0 vs 9.0 days; P=.05). Women taking COC had significantly more days without bleeding during the 14-day treatment period (median 9.0 vs 3.5 days; P=.03). In the COC treatment group, 86% of women experienced recurrence of bleeding within 10 days of COC cessation. There was no continued improvement in bleeding symptoms after COC treatment. This study did not address the amount of daily bleeding, nor classify bleeding patterns after COC treatment.²

KATHRYN FREEMAN, MD
JAMIE D. SANTILLI, MD
UNIVERSITY OF MINNESOTA FAMILY MEDICINE AND COMMUNITY HEALTH
MINNEAPOLIS, MN

1. Abdel-Aleem H, d’Arcangues C, Vogelsong KM, Gülmezoglu AM. Treatment of vaginal bleeding irregularities induced by progestin only contraceptives. *Cochrane Database Syst Rev.* 2007; (4):CD003449.pub3. [STEP 1]
2. Guahhi M, McBride M, Sheeder J, Teal S. Short-term treatment of bothersome bleeding for etonogestrel implant users using a 14-day oral contraceptive pill regimen: a randomized controlled trial. *Obstet Gynecol.* 2015; 126(3):508–513. [STEP 2]

YOUR AD HERE!

Evidence-Based Practice is now advertising for faculty position recruitment and fellowships. We offer competitive pricing for all classified and display ads.

For more information or to have your ad appear in *Evidence-Based Practice*, please contact ebp@fpin.org

Does the use of personal protective equipment (PPE) while examining patients with methicillin-resistant *Staphylococcus aureus* (MRSA) decrease the incidence of nosocomial transmission in the hospital setting?

EVIDENCE-BASED ANSWER

Yes. PPE use is associated with reductions in the colonization rate, infection rate of MRSA, and subsequent antibiotic use (SOR: **B**, observational studies). Also, the use of disposable gowns and gloves for care of selected high-risk patients has been shown to reduce the incidence of nosocomial infection (SOR: **B**, observational studies).

A before-and-after observational study examined prevention and control of multiresistant bacteria in a French teaching hospital of 66,383 admitted medical, surgical, geriatric, and intensive care ward adult patients for a total of 489,602 patient days of hospitalization.¹ The institution implemented a barrier precaution use protocol (hand washing, wearing disposable gloves/gowns) in all wards studied and then analyzed incidence of MRSA over the next 12 months in three 4-month periods.

The average incidence of MRSA infection was 0.89 per 1,000 patient-days (95% CI, 0.81–0.97). The incidence of MRSA decreased overall by 18% between the first and third monitoring periods ($P<.01$), when adjusted for demographics and hospital ward unit.¹

A prospective cohort study used a 2-stage evaluation and intervention program for control of MRSA in the hospital setting.² The first stage evaluated MRSA prevalence in the hospital, and the second stage instituted contact isolation (gloves, hand washing) in 4 hospital units (surgery, orthopedics, adult intensive care unit (ICU), and neonatal ICU) for every patient who tested MRSA positive.

In the 7-month study, MRSA isolates decreased from 45 to 24 ($P=.05$) and the number of patients treated with vancomycin decreased from 31 to 5 ($P=.001$) in the intervention units. A subsequent decrease in MRSA isolates throughout the entire hospital was noted, but the decrease was not statistically significant. The authors concluded that the morbidity and mortality resulting from severe infections with MRSA and the additional associated hospital expenses provide good reasons for implementing contact isolation with MRSA carriers.²

Another prospective cohort study randomly assigned 70 immunocompetent children who required mechanical ventilation in the pediatric ICU to receive either standard care or protective isolation with disposable gowns and gloves, and followed both groups for nosocomial infections.³ Risk factors predisposing to infection in the 2 groups were adjusted and equivalent.

Overall nosocomial colonization with any bacteria occurred sooner (7 vs 12 days; $P<.01$) and led to subsequent infection more often (12 vs 2 patients; $P=.01$) in the standard care group than in the intervention group. Also, time to first infection was longer (median 20 vs 8 days; $P=.04$), the daily infection rate was 2.2 times lower (95% CI, 1.2–4.0), and there were fewer days with fever (13% vs 21%; $P=.001$) in the intervention group, although these data were not specific to MRSA. The authors concluded that the use of disposable gowns and gloves for care of selected high-risk patients reduced the incidence of nosocomial infection.³

EBP

AARON LAMBERT, MD
BRODY SCHOOL OF MEDICINE
EAST CAROLINA UNIVERSITY
GREENVILLE, NC

1. Eveillard M, Eb F, Tramier B, Schmit JL, Lescure FX, Biendo M, et al. Evaluation of the contribution of isolation precautions in prevention and control of multi-resistant bacteria in a teaching hospital. *J Hosp Infect.* 2001; 47(2):116–124. [STEP 2]
2. Mishal J, Sherer Y, Levin Y, Katz D, Embon E. Two-stage evaluation and intervention program for control of methicillin-resistant *Staphylococcus aureus* in the hospital setting. *Scand J Infect Dis.* 2001; 33(7):498–501. [STEP 2]
3. Klein BS, Perloff WH, Maki DG. Reduction of nosocomial infection during pediatric intensive care by protective isolation. *N Engl J Med.* 1989; 320(26):1714–1721. [STEP 2]



Interested in reading more HDAs?

Visit www.fpin.org/ebparchives and click on this month's issue to access the online content.

What is the appropriate dose for spironolactone as a fourth-line agent in treating resistant hypertension?

Bottom line

In patients with resistant hypertension, 48% to 73% can be controlled by adding 25 to 50 mg spironolactone. Increasing to 100 mg may not have any more effect (SOR: **C**, RCT and cohort study with disease-oriented outcomes).

Evidence summary

A multicenter, double-blind RCT including 161 patients with resistant hypertension evaluated the addition of low-dose spironolactone.¹ Patients were older than 18 years and had office systolic blood pressure (SBP) >140 mmHg or office diastolic blood pressure (DBP) >90 mmHg despite being on at least 3 different classes of antihypertensive medications. Patients were randomized to 25 mg spironolactone daily or placebo. Blood pressure was evaluated before starting treatment and 4 and 8 weeks after starting the treatment.

From baseline to 8 weeks, spironolactone reduced SBP (−9.8 mmHg; 95% CI, −14 to −5) and DBP (−3.2 mmHg; 95% CI, −6 to −0.5) more than placebo. More patients taking spironolactone (73%) reached the goal of SBP <140 mmHg and DBP <90 mmHg than placebo patients (41%), with a number to treat of 3 ($P=0.001$). Adverse events with spironolactone treatment included slight fluctuations of electrolyte levels and kidney function, such as a decrease in sodium level, increased potassium level, and increased serum urea and creatinine. Albuminuria and proteinuria decreased with spironolactone treatment. Both groups had a small comparable weight gain.¹

A prospective cohort trial, conducted between April 2007 and September 2008, assessed the effectiveness of spironolactone in 175 patients with resistant hypertension, defined as the failure to control office BP (>140/90 mmHg) despite a treatment with more than 3 different classes of antihypertensive drugs in optimal dosages.² Mean age was approximately 62 years, mean body mass index was 30.2 kg/m². About 72% of patients were women, 33% had diabetes, 85% had dyslipidemia, and 52% had previous cardiovascular diseases. Exclusion criteria included a baseline serum creatinine level >1.5 mg/dL or potassium >5.5 mmol/L. Patients with primary aldosteronism were not included.

Initially, 236 eligible patients had 24-hour ambulatory BP monitoring, after which 175 patients were classified as having resistant hypertension (mean 24-hour BP >130/80 mmHg). Spironolactone 25 mg/d was started in these 175 patients. Follow-up visits were scheduled at 2, 4, and 6 months and included assessment of tolerance to treatment, office BP measurements, and serum creatinine and potassium evaluation. Depending on these results, the spironolactone dose was then titrated up to 50 or 100 mg during this period. A second ambulatory BP test was obtained at around 7 months.²

The mean decrease in 24-hour SBP and DBP associated with spironolactone was 16 mmHg (95% CI, 13–18) and 9 mmHg (95% CI, 7–10), respectively. Controlled ambulatory BP monitoring was reached in 48% of patients. Patients using 100 mg/d spironolactone (31 patients) did not have greater BP reduction in office or ambulatory testing than patients using 25 to 50 mg/d. Some of the adverse events (observed in 7.4% of patients) that led to discontinuation of spironolactone included gynecomastia, libido reduction, electrolyte abnormality, and acute renal failure.² **EBP**

KUSHAN MOONESINGHE, MD
KHYATI TALATI, MD
SIU FAMILY MEDICINE
CARBONDALE, IL

REFERENCES

1. Václavík J, Sedlák R, Jarkovský J, Kociánová E, Táborský M. Effect of spironolactone in resistant arterial hypertension: a randomized, double-blind, placebo-controlled trial (ASPIRANT-EXT). *Medicine (Baltimore)*. 2014; 93(27):e162. **[STEP 2]**
2. de Souza F, Muxfeldt E, Fiszman R, Salles G. Efficacy of spironolactone therapy in patients with true resistant hypertension. *Hypertension*. 2009; 55(1):147–152. **[STEP 3]**

EVIDENCE YOU CAN TRUST

The members of FPIN are deeply committed to providing accurate, unbiased, and evidence-based information that will help physicians provide better care to their patients – without the influence of industry support.

You can trust that *Evidence-Based Practice* is completely independent of pharmaceutical industry influence.

EVIDENCE-BASED PRACTICE

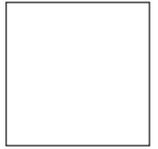
Family Physicians Inquiries Network, Inc.

401 West Boulevard North

Suite D

Columbia, MO 65203

Change Service Requested



YOUR AD HERE

Evidence-Based Practice is now advertising for faculty position recruitment and fellowships. We will run a listing of all positions available every 6 months.

Prefer to have the space all to yourself or need your ad to appear more quickly? We offer competitive pricing for classified and display ads.

Evidence-Based Practice is circulated to 5,000 family physicians, faculty, and residents monthly. For more information or to have your ad appear in *Evidence-Based Practice*, please contact ebp@fpin.org.



EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the
Family Physicians Inquiries Network

In patients with acute gouty attacks, should allopurinol be started immediately or delayed?

EVIDENCE-BASED ANSWER

Starting allopurinol immediately may not have large adverse effects on duration, severity, or recurrence of acute gouty attacks (SOR: **B**, limited-quality noninferiority RCTs). In patients who are candidates for allopurinol, allopurinol 100 mg daily may be started with colchicine 0.6 mg BID at the onset of an acute flare, with a goal of titrating allopurinol up after 2–5 weeks (SOR: **C**, consensus guideline).

A double-blinded RCT of 31 predominantly middle-aged men with crystal-proven acute gout and an indication for urate-lowering therapy evaluated the effect of allopurinol when initiated during an acute attack.¹ All patients received colchicine 0.6 mg BID and either allopurinol titrated up from 100 to 200 mg after 14 days or a 28-day matched placebo. The duration of acute gouty attacks were assessed by clinicians in days from time of enrollment.

A significant reduction of uric acid levels after 28 days with allopurinol was observed compared with placebo (6.4 vs 8.3 mg/dL; $P=.012$). Per-protocol statistical evaluation showed no increase in attack duration with allopurinol versus placebo (15.4 vs 13.4 days; $P=.5$). Post hoc analysis revealed the study to be underpowered to detect a quarter of one standard deviation change, which would have required 116 participants in each group.¹

An RCT evaluated the administration of allopurinol during acute gout attacks, effects on pain over the first 10 days, and whether delaying allopurinol administration decreases acute flare recurrence.² The 30-day study consisted of 51 middle-aged male veterans with primary gout without tophaceous

gout. All received indomethacin 50 mg TID for 10 days and colchicine 0.6 mg BID for 90 days. For the first 10 days of the study, 300 mg allopurinol was given only to the immediate-treatment group; a placebo was given to delayed-treatment group. On day 11, allopurinol 300 mg was also given to the delayed-treatment group. Pain was evaluated by self-reported pain diaries using 10-point visual analog scale (VAS).

The mean VAS scores were similar between allopurinol and placebo at day 0 (6.7 vs 6.3; $P=.37$) and at day 10 (0.18 vs 0.27; $P=.54$). This study had a 92% power to detect a 20% pain difference, which was chosen by the authors to represent a clinically relevant difference. Recurrence of self-reported acute flares occurring during the study were statistically insignificant between the immediate and delayed allopurinol groups (7.7% vs 12%; $P=.61$).²

The 2012 American College of Rheumatology guidelines stated that pharmacological urate-lowering therapy, including allopurinol, may be started during an acute gout attack when used concurrently with colchicine 0.6 mg BID.³ The guidelines stated that allopurinol should be started at no more than 100 mg daily, to be titrated up every 2–5 weeks. The guidelines were based on a literature review and consensus among an international expert panel.^{3,4}

MICHAEL HALL, MD
MARIA SAN-JUAN, MD
ANTHONY VETTRAINO JR., MD
ST. MARY MERCY HOSPITAL FMR
LIVONIA, MI

1. Hill EM, Sky K, Sit M, Collamer A, Higgs J. Does starting allopurinol prolong acute treated gout? A randomized clinical trial. *J Clin Rheumatol*. 2015; 21(3):120–125. [STEP 2]
2. Taylor TH, Mecchella JN, Larson RJ, Kerin KD, Mackenzie TA. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. *Am J Med*. 2012; 125(11):1126–1134. [STEP 2]
3. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012; 64(10):1431–1446. [STEP 1]
4. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)*. 2012; 64(10):1447–1461. [STEP 1]

Are statins beneficial for primary prevention in adults with an elevated hs-CRP and an intermediate Framingham CVD risk score?

EVIDENCE-BASED ANSWER

Statin therapy for cardiovascular primary prevention significantly reduces morbidity and mortality (estimated 5-year number needed to treat [NNT] between 18 and 40) in adults with an intermediate Framingham cardiovascular risk score and a high-sensitivity C-reactive protein (hs-CRP) level ≥ 2 mg/L (SOR: **B**, RCT and systematic review of prospective cohort studies).

A double-blinded RCT evaluated 17,802 adults (men aged ≥ 50 years, women aged ≥ 60 years) with an LDL < 130 mg/dL and an elevated hs-CRP ≥ 2 mg/L who received either rosuvastatin 20 mg or placebo and were monitored for adverse outcomes (nonfatal myocardial infarction [MI], nonfatal stroke, hospitalization for unstable angina, cardiovascular revascularization, or cardiovascular death).¹ The trial was stopped after a median follow-up of 1.9 years because of significantly favorable outcomes in the intervention group.

When the data were analyzed based on Framingham scores, a significant decrease was noted in adverse outcomes (as listed above) compared with placebo for patients in the rosuvastatin group with a 5% to 10% 10-year Framingham cardiovascular disease (CVD) risk (hazard ratio [HR] 0.55; 95% CI, 0.36–0.84; 5-year NNT=40) and among adults with an 11% to 20% Framingham risk (HR 0.51; 95% CI, 0.39–0.68; 5-year NNT=18). Limitations to this study included the relatively short duration of follow-up, its pharmaceutical support, and the lack of a comparable arm to evaluate statins for adults with intermediate-risk scores and a low hs-CRP.¹

A systematic review analyzing data from 52 prospective cohort studies (N=246,669) assessed the levels of CRP for the prediction of first cardiovascular events (MI, fatal coronary heart disease, or stroke).² These studies included 13,199 patients categorized as intermediate risk (10%–20% CVD risk).

The review found that an assessment of CRP with initiation of statin therapy within this group could help prevent approximately 30 additional cardiovascular events over a period of 10 years or 1 additional event per every 440

people screened, resulting in 23 additional people starting statin therapy (number needed to assess=440, NNT=23). This review was limited by a lack of complete information on statin use, heterogeneity between studies, and from the use of cohort studies rather than RCTs.²

ANNAMARIE MACKEY, MD
JENNIFER HOOK, MD, MPH
 GROUP HEALTH FMR
 SEATTLE, WA

1. Ridker PM, MacFadyen JG, Nordestgaard BG, Koenig W, Kastelein JJ, Genest J, et al. Rosuvastatin for primary prevention among individuals with elevated high-sensitivity C-reactive protein and 5% to 10% and 10% to 20% 10-year risk. Implications of the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial for “intermediate risk.” *Circ Cardiovasc Qual Outcomes*. 2010; 3(5):447–452. [STEP 2]
2. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med*. 2012; 367(14):1310–1320. [STEP 3]

What is the best screening instrument for detecting patients with panic disorder in the primary care setting?

EVIDENCE-BASED ANSWER

The Panic Disorder Module of the Patient Health Questionnaire (PHQ) has a higher specificity (96%–99%) and sensitivity (75%–81%) for detecting panic disorder than other studied screening instruments (SOR: **A**, systematic review of prospective studies).

In 2014, a systematic review of 13 prospective studies with 2,647 patients compared 9 different screening instruments for detecting generalized anxiety or panic disorder in primary care settings based on self-reported information.¹ Four studies including 1,731 patients were assessed for identifying patients with panic disorder, while the other studies evaluated tools for the detection of generalized anxiety disorder. Diagnostic interviews were used as the gold standard in diagnosis of panic disorder in all the studies (who conducted the interviews was not provided).

The Panic Module of the PHQ (consisting of 5 questions) had a higher specificity (99%) and positive likelihood ratio (LR+ 78) than the Brief Panic Disorder Screen (BPDS), Symptom Driven Diagnostic System for Primary Care (SDDS-PC), the Beck Anxiety Inventory–Primary Care (BAI-PC), the Primary Care Evaluation of Mental Disorders (PRIME-MD), and

TABLE

Accuracy of instruments in diagnosing panic disorders

	No. of trials	Total N	Sensitivity (%)	Specificity (%)	LR+	LR-
Systematic review¹	13	2,647				
PHQ	1	585	81	99	78	0.20
SDDS-PC	3	1,146	78	67	7.9	0.33
10-item scale	1	124	72	71	2.4	0.4
BPDS	1	295	61	29	0.86	1.36
BAI-PC	1	56	85	81	4.6	0.19
PRIME-MD	1	431	93	53	2.0	0.12
Cohort study²	1	499				
PHQ	—	—	75	96	18.75	0.26
HADS	—	—	91	62	2.39	0.13
Single panic question	—	—	93	78	4.22	0.09

BAI-PC=Beck Anxiety Inventory-Primary Care; BPDS=Brief Panic Disorder Screen; HADS=Hospital Anxiety and Depression Scale; LR+=positive likelihood ratio; LR-=negative likelihood ratio; PHQ=Patient Health Questionnaire; PRIME-MD=Primary Care Evaluation of Mental Disorders; SDDS-PC=Symptom Driven Diagnostic System for Primary Care.

an unnamed 10-item scale for detecting panic disorder in the studied populations (see **TABLE**).¹

A prospective cohort study in 2002 compared several screening questionnaires with the Structured Clinical Interview for DSM-IV (SCID) that was used as the gold standard for the diagnosis of panic disorder among a population of 499 patients.² This population comprised 348 medical outpatients and 151 patients from the psychosomatic outpatient clinic. The study was not included in the 2014 systematic review because of the psychosomatic patients. The study compared the Hospital Anxiety and Depression Scale (HADS), the PHQ questions for panic disorder, a single screening question, and physician diagnosis.

Of all measures, the Panic Module of the PHQ had the highest specificity (96%) of any of the other instruments and a positive likelihood ratio of 18.75 (see **TABLE**).

J. MARTY LINSEISEN, MD
AMY TRELEASE-BELL, MD
 MAINE DARTMOUTH FMR
 AUGUSTA, ME

1. Herr NR, Williams JW Jr, Benjamin S, McDuffie J. Does this patient have generalized anxiety or panic disorder? The Rational Clinical Examination systematic review. *JAMA*. 2014; 312(1):78–84. [STEP 2]
 2. Lowe B, Gräfe K, Zipfel S, Spitzer RL, Herrmann-Lingen C, Witte S, et al. Detecting panic disorder in medical and psychosomatic outpatients: comparative validation of the Hospital Anxiety and Depression Scale, the Patient Health Questionnaire, a screening question, and physicians' diagnosis. *J Psychosom Res*. 2003; 55(6):515–519. [STEP 2]

In children 6–10 years old on stimulant therapy for ADHD, how often should blood pressure be measured?

EVIDENCE-BASED ANSWER

The answer is unclear. Stimulant therapy in children with attention deficit hyperactivity disorder (ADHD) causes mild diastolic blood pressure and heart rate elevations and is associated with an increase in adverse cardiovascular (CV) events, but evidence is lacking on the usefulness and frequency of blood pressure monitoring (SOR: **C**, RCTs and cohort studies of disease-oriented evidence)

A 2006 double-blind, placebo-controlled, randomized crossover trial evaluated 13 children (age range 5–15 years) on their “usual dose” of stimulant medication (methylphenidate, dextroamphetamine/amphetamine, or dextroamphetamine) or placebo and measured their blood pressure, heart rate, and rate-pressure product (RPP).¹ The RPP (the product of systolic blood pressure and heart rate) is an index of myocardial oxygen demand. The study had 2 stages of 4 days each, for a total of 8 days. In stage 1,

TABLE 1

Ambulatory blood pressure and heart rate effects of stimulants compared with placebo¹

Variable	Placebo	Active	P
Systolic blood pressure (mmHg)			
Total	114	117	.169
Wake	122	125	.081
Sleep	103	105	.680
Diastolic blood pressure (mmHg)			
Total	66 ^a	70 ^a	.021
Wake	72 ^a	76 ^a	.029
Sleep	56	59	.209
Heart rate (beats/min)			
Total	80 ^a	86 ^a	.004
Wake	86	93	.110
Sleep	70	65	.374
Rate-pressure product (mmHg×beats/min)			
Total	9,076 ^a	9,958 ^a	.008
Wake	10,389 ^a	11,558 ^a	.010
Sleep	7,199	6,710	.373

^aSignificant difference.

the children received either their usual dose of stimulant or placebo for a 3-day run-in period followed by 24-hour blood pressure and heart rate monitoring. In stage 2, the children received the alternate therapy and monitoring in the same way.

Total diastolic blood pressure, waking diastolic blood pressure, total heart rate, total RPP, and wake RPP were significantly higher during active drug treatment compared with placebo, but systolic blood pressure was no different (see **TABLE 1**). Only 11 children completed both sets of ambulatory testing.¹

A 2001 RCT (N=137) examined the CV effects of methylphenidate and dextroamphetamine/amphetamine (Adderall) in an ADHD referral clinic located in a large urban hospital.² Children (mean age 10.5 years) received placebo or titrated doses of 5, 10, or 15 mg of either methylphenidate or dextroamphetamine/amphetamine. Each of the different doses was given for 1 week and CV monitoring (pulse and

blood pressure) was performed on day 7 of each week for 4 weeks. Each child was randomly assigned to receive the 4 different medication doses in 1 of 6 sequences. Patients were blinded to the sequence but not the medication.

No differences were noted between the methylphenidate or dextroamphetamine/amphetamine groups on any CV measures. The only significant differences were slightly higher diastolic blood pressure (64.0 vs 60.2 mmHg; $P<.05$) and heart rate (84.1 vs 82.4 bpm; $P<.05$) with pooling of the 15-mg dose of both medications compared with baseline measurements. Limitations included the short duration of the study, lack of medication compliance monitoring, and unknown timing of CV assessment after medication dose.²

A 2014 cohort study evaluated the risk of adverse CV events in 8,300 Danish children (mean age 10 years) with ADHD who received stimulant therapy.³ Stimulant (amphetamine, dextroamphetamine, or methylphenidate) therapy was categorized according to daily dose ranges

TABLE 2

Blood pressure and heart rate effects⁴

	Baseline	6 months	P	Baseline	12 months	P	Baseline	24 months	P
	315 patients			194 patients			61 patients		
Methylphenidate-treated patients (n=351)									
Mean SBP	102.58	102.84	.77	103.01	102.52	.65	100.62	99.62	.63
Mean DBP	63.96	64.77	.19	63.85	65.20	.13	63.18 ^a	59.28 ^a	.009
Mean HR	77.76 ^a	79.86 ^a	.01	77.54	78.79	.17	79.86 ^a	76.05 ^a	.02
Atomoxetine-treated patients (n=350)									
Mean SBP	104.3	105.2	.21	104.73	105.09	.73	105.84	107.97	.18
Mean DBP	66.66 ^a	68.27 ^a	.01	67.65	67.78	.87	69.34	70.45	.53
Mean HR	78.46 ^a	81.40 ^a	.001	77.79 ^a	81.05 ^a	.004	79.58	79.79	.92

DBP=diastolic blood pressure; HR=heart rate; SBP=systolic blood pressure.

^aSignificant difference.

of 0–14 mg/d, 15–29 mg/d, and ≥30 mg/d. Children at higher risk of CV events were excluded (congenital heart disease, CV disease before age of 5, fragile X, Down syndrome, parental CV disease, diabetes or a prescription for neuroleptics, CV, or respiratory medications).

Overall, the risk of CV events (hypertension, ischemic heart disease, pulmonary heart disease, arrhythmias, cardiac arrest, heart failure, or CV disease not otherwise specified) was increased in children treated with stimulants compared with children who had similar risk factors but were not on stimulants (hazard ratio [HR] 2.3; 95% CI, 1.2–4.8). The CV event risk was slightly lower at the methylphenidate dose of 15 mg (n=8,298; HR 2.0; 95% CI, 1.0-4.1) compared with the ≥30 mg methylphenidate dose (n=8,295; HR 2.2; 95% CI, 1.2-4.2).³

A 2010 open-label prospective cohort study on Italian youth (N=1,758, mean age 10.7 years) evaluated the CV effects of methylphenidate and atomoxetine.⁴ More than half of the patients were excluded because they had only 1 follow-up visit or a follow-up of <6 months. The mean total daily dose in the methylphenidate group (n=351) was 18.4 mg; the mean total daily dose in the atomoxetine group (n=350) was 38.6 mg.

The CV changes of each medication are summarized in **TABLE 2**. In the methylphenidate group compared with baseline, diastolic blood pressure was slightly lower at 24 months while heart rate was slightly higher at 6 months

but slightly lower at 24 months. In the atomoxetine group compared with baseline, diastolic blood pressure was slightly higher at 6 months and heart rate was slightly higher at 6 and 12 months. No significant changes in systolic blood pressure were noted in either medication at any time period evaluated. Study limitations include a high dropout rate (>50%) and unknown medication adherence.⁴

MOLLY ZAVALA, MD
MARY JO IRONSIDE, MD
AMANDEEP KAUR, MD
 UNIVERSITY OF ILLINOIS FMR
 ROCKFORD, IL

- Samuels JA, Franco K, Wan F, Sorof JM. Effect of stimulants on 24-h ambulatory blood pressure in children with ADHD: a double-blind, randomized, cross-over trial. *Pediatr Nephrol*. 2006; 21(1):92–95. [STEP 2]
- Findling RL, Short EJ, Manos MJ. Short-term cardiovascular effects of methylphenidate and Adderall. *J Am Acad Child Adolesc Psychiatry*. 2001; 40(5):525–529. [STEP 2]
- Dalsgaard S, Kvist AP, Leckmen JF, Nielsen HS, Simonsen M. Cardiovascular safety of stimulants in children with attention-deficit/hyperactivity disorder: a nationwide prospective cohort study. *J Child Adolesc Psychopharmacol*. 2014; 24(6):302–310. [STEP 3]
- Arcieri R, Germinario EA, Bonati M, Masi G, Zuddas A, Vella S, et al. Cardiovascular measures in children and adolescents with attention-deficit/hyperactivity disorder who are new users of methylphenidate and atomoxetine. *Journal of Child and Adolescent Psychopharmacology*. 2012; 22(6):423–431. [STEP 3]

We invite your questions and feedback.
 Email us at **EBP@fpin.org**.

Does weight loss increase libido in obese men with low sex drive?

EVIDENCE-BASED ANSWER

Yes. Consumption of a low-calorie diet for at least 8 weeks resulting in a mean weight loss of 9.5 to 12 kg is associated with an increase in sexual desire in obese men (SOR: **C**, small cohort study). Weight loss (mean body mass index [BMI] decrease of 17–20 kg/m²) achieved through bariatric surgery is also associated with an increase in sexual desire and drive in obese men who have low sex drive compared with nonsurgical controls (SOR: **B**, small cohort studies).

A 2010 cohort study evaluated the effect of an 8-week low-calorie diet on sexual function and lower urinary tract symptoms in 68 obese men (BMI >30 kg/m²).¹ Patients were recruited into the intervention group via advertisements and a control group matched for age and BMI to men without diabetes in the intervention group were recruited similarly. Of the intervention patients, approximately 50% (n=19) had diabetes controlled with diet alone or diet plus metformin (HbA1C <7%). None of the participants in the control group had diabetes. All patients were nonsmokers with mean ages of 58 years in intervention patients with diabetes, 45 years in intervention patients without diabetes, and 48 years in the control group. Exclusion criteria included GFR <60 mL/min/1.73m², pelvic trauma, prostate disease, neuropathy, hypertension, cardiovascular disease, psychiatric illness, recreational drug use, or alcohol consumption over 500 grams per week.

Intervention patients were placed on a low-calorie diet (850–900 kcal/d) using meal replacements twice a day and 1 small meal for 8 weeks. The control group ate their usual diet. Participants completed the 14-item Sexual Desire Inventory (109 points possible, with higher score equating to greater sexual desire) to assess change in sexual desire.¹

Intervention patients both with and without diabetes lost significantly more weight than the controls (nondiabetic intervention group 12 kg; diabetic intervention group 9.5 kg; control group 2.9 kg; *P*<.01 for both comparisons vs control). The Sexual Desire Inventory increased significantly in intervention group compared with the control

group (nondiabetic intervention group 9.1 points; diabetic intervention group 10 points; control group 0.8 points; *P*<.01 for both comparisons vs control).¹

A 2009 cohort study (N=64, all men) compared the effects of bariatric surgery on reproductive function including enjoyment in sexual activity, sexual desire, sexual performance, and sexual encounters.² Mean age was 49 years and mean BMI was 46 kg/m². Of the 64 patients, 22 underwent gastric bypass surgery, 30 were obese controls who were not seeking surgery, and 12 were controls who sought but did not complete surgery.

All participants filled out the 31-item Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire, which assesses 5 domains including sexual life. The 4 questions within the sexual life domain inquire about avoidance of sexual encounters, difficulty with sexual performance, lack of sexual desire, and lack of enjoyment in sexual activity on a 5-point scale from never true to always true (hence, lower scores indicate improvement).²

At the 2-year follow-up, patients in the surgery group had significantly decreased BMI compared with controls (17 vs 0.46 kg/m²; *P*<.001). Patients in the surgery group experienced a significant improvement in all questions in the sexual life domain on the IWQOL-Lite compared with controls (avoid sexual encounters: –1.8 vs 0.0; difficulty with sexual performance: –2.3 vs –0.1; sexual desire: –1.9 vs 0.05; do not enjoy sex: –1.7 vs –0.05; *P*<.001 for all comparisons).²

A 2008 cohort study of 97 morbidly obese men (mean age 48 years, median BMI 51 kg/m²) who underwent gastric bypass surgery compared sexual function with published control data drawn from a random sample of all men 40 to 79 years old in a Minnesota county.³ Of the surgery patients, 51% had diabetes, 70% had hypertension, and 46% were previous or current smokers.

Surgery patients lost an average of 60% of excess weight at 1 year, 66% at 2 years, and the average BMI dropped to 32 kg/m². Before surgery and a minimum of 6 months after surgery, patients completed the Brief Male Sexual Function Inventory; an 11-item, 5-domain questionnaire with 44 possible points evaluating sexual drive (0–8 points), erectile function (0–12 points), ejaculatory function (0–8 points), sexual problems (0–12 points), and sexual satisfaction (0–4 points).³

An improvement in sexual drive was seen from preoperative to postoperative scores (3.9 vs 5.3 points;

$P < .001$). An improvement in sexual satisfaction was also seen from preoperative to postoperative scores (1.6 vs 2.3 points; $P = .002$). Preoperative sexual function of the surgery patients was reported to be significantly lower than that of age-matched published reference controls across all domains, and postoperative scores neared the range of the age-matched published reference controls (data not provided).³

JEFFREY TINGEY, DO
SARAH DALY, DO, FAAFP
UTAH VALLEY FMR
PROVO, UT

1. Khoo J, Piantadosi C, Worthley S, Wittert GA. Effects of a low-energy diet on sexual function and lower urinary tract symptoms in obese men. *Int J Obes (Lond)*. 2010; 34(9):1396–1403. [STEP 3]
2. Hammoud A, Gibson M, Hunt SC, Adams TD, Carrell DT, Kolotkin RL, et al. Effect of Roux-en-Y gastric bypass surgery on the sex steroids and quality of life in obese men. *J Clin Endocrinol Metab*. 2009; 94(4):1329–1332. [STEP 3]
3. Dallal RM, Chernoff A, O’Leary MP, Smith JA, Braverman JD, Quebbemann BB. Sexual dysfunction is common in the morbidly obese male and improves after gastric bypass surgery. *J Am Coll Surg*. 2008; 207(6):859–864. [STEP 3]

In adults with irritable bowel syndrome (IBS), do probiotics improve gastrointestinal symptoms?

EVIDENCE-BASED ANSWER

Yes, but the results do not appear to be dramatic. Probiotics lead to improvement in some global IBS symptom and quality-of-life scores, but inconsistent improvements in individual symptoms of pain and distension and no improvement in other individual symptoms. The most effective dose and probiotic strain/species is unknown (SOR: **A**, meta-analysis of RCTs and individual RCTs).

A 2015 meta-analysis of 15 RCTs (N=1,793) investigated the effectiveness of probiotics versus placebo for the treatment of IBS symptoms.¹ Patients met criteria for IBS based on Rome II, Rome III, the International Classification of Health Problems in Primary Care, or the World Organization of Family Doctors criteria, and trials investigated a variety of symptoms including abdominal pain, bloating, and flatulence. An assortment of probiotic species and doses were included.

“General symptoms,” which were not individually defined, were more likely to be adequately improved, with

an undefined threshold, for patients taking probiotics versus patients taking placebo (7 trials, n=654; relative risk [RR] 2.1; 95% CI, 1.1–4.3). Most of the studies used the IBS symptom severity scale, a clinical measure of pain, distension, bowel dysfunction, and quality of life. Specific thresholds to delineate response were not reported. Patients taking probiotics were more likely to have a response in abdominal pain severity scores than patients taking placebo (2 trials, n=595; RR 2.0; 95% CI, 1.1–3.4). Abdominal pain rated by visual analog scale (0=no pain and 10=worst pain), however, did not differ between probiotics and placebo (2 trials, n=156; weighted mean difference -0.6 ; 95% CI, -1.3 to 0.2). Symptom scales of bloating, distension, and flatulence also did not differ between probiotics and placebo.¹

A 2014 multicenter RCT, published after the search date of the review above, investigated the effect of 2 different doses of probiotics versus placebo on the quality of life of 84 patients with IBS per Rome III criteria.² A mixture of 3 strains of probiotic bacteria were used for 6 weeks: 1 strain of *Pediococcus acidilactis* and 2 strains of *Lactobacillus plantarum* at high (effective dose $1-3 \times 10^{10}$ cfu/capsule) and low ($3-6 \times 10^9$ cfu/capsule) doses. Efficacy was measured using the IBS-quality of life (QoL) questionnaire assessing 9 domains related to quality of life, with a final score on a 0 (lowest quality) to 100 (highest quality) scale. Symptom relief was assessed on a 5-point scale and anxiety related to IBS symptoms was assessed with a validated visceral sensitivity index ranging from 15 to 90, with higher numbers representing greater anxiety.

The mean QoL score improved more at 6 weeks for both low- and high-dose probiotics than for placebo. Mean score improvements were 18 points in the high-dose group, 22 points in the low-dose group, and 9 points in the placebo group ($P < .05$ for both comparisons to placebo). Symptom relief scores were not different between probiotic and placebo. The visceral sensitivity index at 6 weeks improved more in patients treated with probiotics at low dose (14-point improvement) and high dose (10-point improvement) compared with placebo (7-point improvement; $P < .05$ for both comparisons to placebo). No statistically significant difference was noted in sensitivity scores between high- and low-dose probiotics.²

A 2012 RCT, not included in the 2015 meta-analysis mentioned above, investigated the effect of a multistrain

probiotic versus placebo in 60 patients with IBS (per Rome III criteria) over 4 weeks.³ The patients treated with probiotics (*Bifidobacterium longum* and *Lactobacillus acidophilus*) took 2 capsules 3 times daily and the placebo group took 1 placebo capsule 3 times daily. Patients rated 6 IBS symptoms on a 0 to 3 scale and response was classified as effective, ineffective, or worsened based on unreported thresholds.

After 4 weeks, more patients in the probiotics group than the placebo group reported any effective response for time of abdominal pain (84% vs 20%), frequency of abdominal pain (62% vs 26%), time of abdominal distension (73% vs 39%), and frequency of abdominal distension (73% vs 30%; $P < .01$ for all comparisons). No difference was noted between groups for dissatisfaction with defecation.³

LISA KURAJIAN, DO
AMBER GRUBER, DO
 BEAUMONT HEALTH SYSTEM
 TROY, MI

1. Didari T, Mozaffari S, Nikfar S, et al. Effectiveness of probiotic in irritable bowel syndrome: updated systematic review with meta-analysis. *World J Gastroenterol.* 2015; 21(10):3072–3084. [STEP 1]
2. Lorenzo-Zuñiga V, Llop E, Suárez C, et al. I31, a new combination of probiotics, improves irritable bowel syndrome-related quality of life. *World J Gastroenterol.* 2014; 20(26):8709–8716. [STEP 2]
3. Cui S, Hu Y. Multistrain probiotic preparation significantly reduced symptoms of irritable bowel syndrome in a double-blind placebo-controlled study. *Int J Clin Exp Med.* 2012; 5(3):238–244. [STEP 2]

Are benzodiazepines effective for treatment of generalized anxiety disorder?

EVIDENCE-BASED ANSWER

Benzodiazepine therapy produces a small reduction in generalized anxiety disorder (GAD) symptoms for up to 8 weeks (SOR: **A**, based on 2 systematic reviews of RCTs). However, benzodiazepines are not recommended as a treatment for GAD except in short-term crisis situations (SOR: **C**, expert opinion).

A systematic review examining the effectiveness of pharmacologic treatments for adults with GAD found 4 RCTs (N=1,379) comparing benzodiazepines with placebo.¹ The benzodiazepines used in these 4 trials were alprazolam (2 mg/d), diazepam (15 mg/d), and lorazepam (6 mg/d).

Participants had been diagnosed with GAD via DSM-III-R, DSM-IV, or ICD-10 criteria. The duration of the trials ranged from 4 to 8 weeks.

The main outcome was change in Hamilton Anxiety Scale scores derived from a 14-item questionnaire, in which each item is scored on a scale of 0 (not present) to 4 (severe). The total score range is 0 to 56, with <17 rated as mild, 18 to 24 “mild to moderate,” and 25 to 30 “moderate to severe.”¹

Participants in the benzodiazepine group, who had baseline scores between 23.9 and 28.4, had a reduction of 11.6 to 15.3 points. Patients in the placebo groups, who had baseline scores between 22.9 and 29.3, showed only a 6.7- to 13.1-point decrease. Pooling the results from these 4 trials yielded an effect size of 0.38 for benzodiazepines compared with placebo ($P < .0001$).¹ (An effect size of 0.2 is considered small and 0.6 is considered moderate.)

One limitation of these trials was the short length of the treatment, with a maximum of 8 weeks for this chronic illness. Authors of the systematic review indicated that the results of the individual trials are consistent despite heterogeneity of study design, patient populations, and dosing. Dropout rates and side effects were not discussed in the review.¹

A systematic review analyzed 33 RCTs (N=3,961) examining the effectiveness of benzodiazepines compared with placebo for adults with GAD diagnosed by DSM-II, DSM-III, DSM-III-R, DSM-IV, or ICD-10 criteria.² The benzodiazepines used in these trials were adinazolam, alprazolam, bromazepam, clonazepam, clorazepate, diazepam, etizolam, ketazolam, lorazepam, and triazolam, at varying doses not specified in the systematic review.

Meta-analysis of the 33 RCTs estimated that the benzodiazepine group had lower Hamilton scores compared with the control group, with a mean effect size of 0.32 (confidence interval and P values not provided). The mean absolute baseline and posttreatment Hamilton scores were not reported. Limitations to the RCTs included small study sizes, high dropout rates (21% in benzodiazepine group), short treatment durations (2–4 weeks), and concern for publication bias (smaller trials had higher effect sizes). Side effects were not mentioned. Compared with the first systematic review above, which included 4 trials, this systematic review of 33 studies used broader diagnostic criteria (including earlier DSM versions) and broader population inclusion criteria (including comorbid anxiety and depression).²

A 2011 National Collaborating Centre for Mental Health and National Collaborating Centre for Primary Care evidence-based guideline recommended cognitive behavioral therapy, applied relaxation, or drug therapy with a selective serotonin reuptake inhibitor as first-line treatment for GAD; benzodiazepines were not recommended in the primary care setting, except as short-term treatment during crises.³

RAVI KALWANI, MD
JOHN VAN BUSKIRK, DO
 TACOMA FMRP
 TACOMA, WA

1. Hidalgo RB, Tupler LA, Davidson JR. An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. *J Psychopharmacol*. 2007; 21(8):864–872. [STEP 1]
2. Mitte K, Noack P, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. *J Clin Psychopharmacol*. 2005; 25(2):141–150. [STEP 1]
3. National Institute for Health and Care Excellence (NICE). Generalised anxiety disorder and panic disorder in adults: management. Clinical guideline no. 113. <https://www.nice.org.uk/guidance/cg113>. Published January 2011. Accessed May 25, 2017. [STEP 5]

Does supplemental calcium reduce risk of fractures?

EVIDENCE-BASED ANSWER

Calcium 1,200 mg daily with or without vitamin D decreases all-site fractures in postmenopausal women (SOR: **A**, meta-analysis of RCTs). The effect of calcium 1,000 mg daily plus vitamin D is unclear. Calcium does not have an effect on fractures in men in the short term (SOR: **B**, single RCT). Calcium supplementation for the primary prevention of fractures in noninstitutionalized postmenopausal women is not recommended (SOR: **B**, systematic review of inconsistent RCTs and cohort studies).

A 2007 meta-analysis of 29 RCTs (N=63,897) evaluated the use of calcium supplementation (mean duration of treatment 3.5 years) to reduce the risk of fractures of all types.¹ Studies included patients older than 50 years (mean age 68 years), of whom 92% were women with a baseline fracture risk of 16%. Outcomes included fractures of all types and change in bone mineral density (BMD) from baseline.

A daily calcium dose (most commonly 1,200 mg) alone or in combination with vitamin D (most commonly 800 IU) reduced all types of fractures by 12% (17 trials, n=52,625; relative risk [RR] 0.88; 95% CI, 0.83–0.95). The difference

in RR between calcium-only supplementation (n=6,517) and calcium with vitamin D (n=46,108) was not significantly different (RR 0.87 vs 0.90; *P*=.63).¹

A 2013 follow-up study reported the outcomes of the 86% of women (N=29,862) who were followed for 5 additional years after an RCT (N=36,282) that evaluated the efficacy of 1,000 mg calcium with 400 IU vitamin D versus placebo for prevention of hip fracture, initially over 7 years.² Women who consented to continue in the follow-up study were generally younger, more likely to be white, slightly less likely to have a history of stroke or myocardial infarction or to be obese, and reported higher education and higher use of calcium and/or vitamin D supplementation than women who did not re-consent. All were postmenopausal.

In the initial RCT and in both time periods combined, no difference was noted in hip fracture rates between women taking calcium plus vitamin D supplements compared with placebo. In the postintervention period alone, no difference was noted in hip fractures between groups (hazard ratio [HR] 0.95; 95% CI, 0.78–1.2), but a slight reduction was noted in vertebral fractures in the supplement group versus placebo (HR 0.83; 95% CI, 0.71–0.98).²

A 2013 analysis of the initial RCT trial above with a prospective cohort study including 93,676 postmenopausal women further examined the health benefits and risks of calcium and vitamin D supplementation.³ Combined analyses of data from both the RCT and cohort study demonstrated an overall reduction in hip fracture in women taking calcium and vitamin D (HR 0.65; 95% CI, 0.44–0.98).

A 2008 RCT of 323 healthy men evaluated the effect of 1,200 mg calcium, 600 mg calcium, or placebo on BMD and fractures.⁴ There was a small but significant 1% to 1.5% increase from baseline in BMD of the lumbar spine (*P*=.03) after 6 months in the 1,200 mg supplementation group, but no difference from baseline in the 600 mg and placebo groups. No difference was noted in the number of fractures among the groups (4 in the 1,200 mg/d group, 5 in the 600 mg/d group, and 8 in the placebo group; *P*=.43).

In 2013, the US Preventive Services Task Force (USPSTF) published their recommendation statement on the use of vitamin D and calcium supplementation to prevent fractures in adults based on a systematic review of RCTs and prospective cohort studies.⁵

The USPSTF assigned a Grade D (not recommended) rating to daily supplementation with ≤400 IU vitamin D₃ and

≤1,000 mg calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women. They assigned a Grade I (insufficient evidence) rating to daily supplementation with >400 IU vitamin D₃ and >1,000 mg calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women. They also assigned a Grade I rating to combined vitamin D and calcium for primary prevention of fractures in premenopausal women or in men.⁵

TYLER S. ROGERS, MD

ROGER HOLLAND, MD, PHD

DWIGHT D. EISENHOWER ARMY MEDICAL CENTER

FORT GORDON, GA

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. Tang BM, Eslick GD, Nowson C, et al. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet*. 2007; 370(9588):657–666. [STEP 1]
2. Cauley JA, Chlebowski RT, Wactawski-Wende J, et al. Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. *J Womens Health (Larchmt)*. 2013; 22(11):915–929. [STEP 2]
3. Prentice RL, Pettinger MB, Jackson RD, et al. Health risks and benefits from calcium and vitamin D supplementation: women's health initiative clinical trial and cohort study. *Osteoporosis Int*. 2013; 24(2):567–580. [STEP 2]
4. Reid IT, Ames R, Mason B, et al. Randomized control trial of calcium in healthy, non-osteoporotic men. *Arch Intern Med*. 2008; 168(20):2276–2282. [STEP 2]
5. U.S. Preventive Services Task Force. Final update summary: vitamin D and calcium to prevent fractures: preventive medication. <http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/vitamin-d-and-calcium-to-prevent-fractures-preventive-medication>. Published February 2013. Accessed April 26, 2017. [STEP 1]

Is *Helicobacter pylori* infection associated with chronic headache (specifically migraine)?

EVIDENCE-BASED ANSWER

Perhaps. Compared with patients without migraines, patients with migraine have a higher prevalence of *H pylori* infection, especially patients without a family history of migraine (SOR: **B**, meta-analysis of case-control and cross-sectional studies). Eradication of *H pylori* may also decrease the disability, frequency, duration, and magnitude of migraine headaches (SOR: **B**, RCT and cohort study).

A meta-analysis in 2014 of 5 case-control and cross-sectional studies evaluated the prevalence of *H pylori* infection in 467 patients with migraines and 436 healthy controls.¹ All the

studies used serum ELISA, urea breath test, and biopsy as single or combination detection methods. The prevalence of *H pylori* was higher in patients with migraine than in patients without migraine (33% vs 45%; $P=.001$; odds ratio [OR] 1.9; 95% CI, 1.1–3.5).

A case-control study in 2007 compared 49 migraineurs without aura to 51 nonmigraineurs to examine the correlation with *H pylori* infection determined by gastric biopsy.² This study included in the above review is summarized separately because migraineurs were further divided by family history of migraine.

H pylori infection was more prevalent in patients with migraine versus without migraine (61% vs 37%; OR 2.6; 95% CI, 1.1–5.9). There was also a higher prevalence of *H pylori* infection in migrainous patients without a family history of migraine versus patients with a family history (81% vs 36%; $P=.001$).²

A 2012 double-blind RCT with 64 migraineurs with positive *H pylori* IgA and IgG studied the effect of *H pylori* treatment on migraines.³ All were given similar acute and prophylactic migraine regimens. The treatment group additionally received *H pylori* triple drug therapy for 4 weeks followed by eradication confirmation with a urea breath test; the control group received placebo. Migraines were assessed before and after with the Migraine Disability Assessment (MIDAS) Questionnaire (0=no disability, 21=severe disability).

A significantly greater reduction in MIDAS scores was observed in the treatment group than in the placebo group (mean reduction of 8 vs 5 points; $P=.05$).³

A cohort study in 2001 examined 148 known migraineurs over a 12-month period to assess change in migraine characteristics after *H pylori* eradication.⁴ The 62 patients with *H pylori* who underwent eradication therapy were compared with 86 *H pylori*-negative patients. Migraine intensity (scale 1–4), duration in hours, and frequency (days per month) were assessed at 2, 4, 6, and 12 months.

Migraine intensity for the control versus posteradication groups were similar at baseline, but the eradication group subsequently had lower scores: 2.8 versus 2.0 at 2 months ($P<.01$); 3.0 versus 1.5 at 4 months ($P<.01$); 3.0 versus 1.4 at 6 months ($P<.01$); and 2.9 versus 1.2 at 12 months ($P<.01$). Migraine duration for the control versus posteradication groups were similar at baseline and 2 months, but were subsequently lower in the eradication group: 15.5 versus

10 hours at 4 months ($P<.05$); 15.2 versus 9 hours at 6 months ($P<.05$); and 15.5 versus 8 hours at 12 months ($P<.01$). Mean frequency for control versus posteradication groups was similar at baseline and 2 months, but subsequently lower in the eradication group: 7.5 versus 4.5 days at 4 months ($P<.05$); 7.4 versus 4.0 days at 6 months ($P<.01$); and 7.9 versus 3.8 days at 12 months ($P<.01$).⁴

SALVATORE BERTUCCI, DO

SHARI SAMMS, MD

CARL R. DARNALL FMR CENTER

KILLEEN, TX

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. Su J, Zhou X, Zhang G. Association between *Helicobacter pylori* infection and migraine: a meta-analysis. *World J Gastroenterol*. 2014; 20(40):14965–14972. [STEP 2]
2. Yiannopoulou KG, Efthymiou A, Karydakos K, Arhimandritis A, Bovaretos N, Tzivras M. *Helicobacter pylori* infection as an environmental risk factor for migraine without aura. *J Headache Pain*. 2007; 8(6):329–333. [STEP 2]
3. Faraji F, Zarinfar N, Zanjani AT, Morteza A. The effect of *Helicobacter pylori* eradication on migraine: a randomized, double blind, controlled trial. *Pain Physician*. 2012; 15(6):495–498. [STEP 2]
4. Gabrielli M, Franceschi F, Fiore G, Candelli M, Armuzzi A, Ojetti V, et al. Beneficial effects of *Helicobacter pylori* eradication on migraine: a 12-month follow-up study. *J Headache Pain*. 2001; 2(1):39–43. [STEP 3]

In patients with localized acute soft tissue or musculoskeletal pain, does topical lidocaine provide better temporary pain relief than topical NSAIDs?

EVIDENCE-BASED ANSWER

The answer is unknown, but both topical agents appear effective. Topical NSAIDs provide a 50% reduction in acute musculoskeletal pain about 1.3 to 1.6 times more often than placebo (SOR: **A**, meta-analysis of RCTs). Although not evaluated for acute musculoskeletal pain, topical lidocaine patches provide at least a 50-point reduction in pain on a 100-point scale in patients with myofascial pain syndrome (SOR: **B**, RCT). The lack of head-to-head comparisons precludes determining which treatment is better.

A 2015 systematic review of 61 RCTs (N=8,386) compared topical NSAIDs with placebo or other active treatment for the management of musculoskeletal pain of at least moderate intensity, lasting <3 months, associated with injuries due to

overuse or strains, sprains, and contusions in adults.¹ The primary outcome was “clinical success,” defined as at least 50% pain relief at 7 days. Ten RCTs (n=2,050) analyzed topical formulations of diclofenac compared with placebo; the formulations of diclofenac included 1% plaster 1 to 2 times per day, 1.16% to 2.32% gel 2 g 2 to 4 times daily, and 4% spray gel 4 to 5 sprays 3 times daily.

Pooled analysis found that 74% of participants treated with topical diclofenac experienced clinical success versus 47% with placebo (risk ratio [RR] 1.6; 95% CI, 1.5–1.7; number needed to treat [NNT]=4). Topical ibuprofen 5% cream or 5% gel used 3 to 4 times daily had a 55% success rate compared with 33% for placebo (5 RCTs, n=436; RR 1.6; 95% CI, 1.3–2.0; NNT=5). Topical ketoprofen plaster used once daily or gel (1%, 2.5%, 5%) used 1 to 3 times daily led to a 73% success rate compared with 47% for placebo (7 RCTs, n=683; RR 1.6; 95% CI, 1.4–1.8; NNT=4). Topical piroxicam 0.5% 1 g 3 to 4 times daily had a 68% clinical success rate versus 47% for placebo (3 RCTs, n=504; RR 1.5; 95% CI, 1.3–1.7; NNT=5). Topical indomethacin 1% 1 g 3 to 4 times daily led to clinical success in 58% of patients compared with 46% with placebo (3 RCTs, n=341; RR 1.3; 95% CI 1.0–1.6; NNT=9).¹

In a 2009 RCT, 60 adults with myofascial pain syndrome who had at least 1 trigger point responsible for a spontaneous pain complaint were randomly allocated to receive a 5% lidocaine patch, a placebo patch, or anesthetic infiltration of a trigger point.² The lidocaine and placebo patches were applied to a trigger point and a control area for 4 days, with replacement every 12 hours.

Patients were evaluated pre-intervention and on days 5 and 9 by measuring the mean number of pain attacks in the previous 4 days, as well as assessing pain at rest, pain on movement, and interference with activities, mood, and quality of life due to pain using a 100-mm visual analog scale (VAS). A pain attack was defined as a spontaneous pain complaint resulting from a periodic exacerbation of a constant ache. The baseline level of pain for all participants in the study was above 40 mm on the VAS.²

Lidocaine patches reduced the mean number of pain attacks from 4.7 per day to 0.8 per day on day 5 and 0.2 per day on day 9 ($P<.001$ for both comparisons). Lidocaine patches reduced mean VAS measurements of pain at rest, pain on movement, and interference with daily activity, work activity, mood, and quality of life all by >50 mm (range 54–62) from baseline by day 5 and by >60 mm (range 61–78)

by day 9 ($P<.001$ for all comparisons). Participants who were treated with the placebo patch did not experience a change in any of the outcomes and lidocaine patch was reported to be significantly better than placebo in all measures.²

INYANGA MACK COLLINS, MD
MOHAMMAD AHMED, MD
ASMA ALGHAMDI, MD
WELISANE BEBE, MD
 BRONX-LEBANON HOSPITAL CENTER FPRP
 BRONX, NY

1. Derry S, Moore RA, Gaskell H, McIntyre M, Wiffen PJ. Topical NSAIDs for acute musculoskeletal pain in adults. *Cochrane Database Syst Rev.* 2015; (6):CD007402. [STEP 1]
2. Affaitati G, Fabrizio A, Savini A, Lerza R, Tafuri E, Costantini R, et al. A randomized, controlled study comparing a lidocaine patch, a placebo patch, and anesthetic injection for treatment for trigger points in patients with myofascial pain syndrome: evaluation of pain and somatic pain thresholds. *Clin Ther.* 2009; 31(4):705–720. [STEP 2]

What are the indications for treatment of hypercholesterolemia with statin therapy in obese children?

EVIDENCE-BASED ANSWER

After 6 months of dietary and lifestyle modifications, statin therapy should be considered for children 11 to 21 years old with a BMI ≥ 97 th percentile and LDL-C ≥ 160 mg/dL or if LDL-C is between 130 and 160 mg/dL and other risk factors or conditions are present. For similar children with BMI between 95th and 97th percentile, statin therapy should be considered if LDL ≥ 130 mg/dL if other risk factors or conditions are present (SOR: **C**, meta-analysis of RCTs with disease-oriented outcomes and evidence-based guideline).

A 2014 systematic review of 8 RCTs (N=1,074) assessed the safety and efficacy of statins in children with familial hypercholesterolemia.¹ The patients were children up to 18 years old followed on statin therapy up to 2 years. Statins included lovastatin 40 mg, pravastatin 5 to 40 mg, simvastatin 20 and 40 mg, atorvastatin 10 to 20 mg, and rosuvastatin 5 to 20 mg.

Five studies (N=566) found that compared with placebo, statins significantly reduced serum LDL (–31.2%; 95% CI, –34.9 to –29.4) and total cholesterol (–26.5%; 95% CI, –28.5 to –24.5), while increasing HDL (3.1%; 95% CI, 0.55–

5.7). Statins also significantly reduced biomarkers for early atherosclerosis compared with placebo.¹

One RCT (n=214) found a small decrease in the carotid intima media thickness of –0.01 mm (95% CI, –0.03 to –0.00) in the statin group, and another RCT (n=175) found a 2.70% (95% CI, 0.42–4.98) improvement in the flow-mediated dilation of the brachial artery in the statin group. Compared with placebo, statins did not affect growth or maturation, and no significant adverse events or myopathies were reported. No differences were noted in liver enzymes or creatinine kinase. The review found no studies directly measuring cardiovascular event risk reduction from statin therapy initiated in childhood.¹

The 2012 National Heart Lung and Blood Institute’s (NHLBI) evidence-based *Guidelines for Cardiovascular Health and Risk Reduction for Children* offered recommendations on the indications for statin therapy.²

Based on the 1992 National Cholesterol Education Program report on blood cholesterol in children, the NHLBI guidelines identified obesity (BMI between the 95th and 97th percentile) and morbid obesity (BMI ≥ 97 th percentile) as medium- and high-level risk factors, respectively, for developing cardiovascular disease and early morbidity due to adverse cardiovascular events.²

The guideline recommended dietary management as the cornerstone to primary prevention of cardiovascular disease in obese children with hyperlipidemia, based on grade A evidence (“well-designed randomized controlled trials [RCTs] or diagnostic studies performed on a population similar to the guidelines’ target population”). If the LDL-C goal (<130 mg/dL) cannot be met after 6 months, the guideline recommended statin therapy in children older than 10 years. The guideline recommended children with LDL-C levels ≥ 250 mg/dL or TG ≥ 500 mg/dL, or who were refractory to statin therapy be referred to a lipid specialist (grade B, “RCTs or diagnostic studies with minor limitations; genetic natural history studies; overwhelmingly consistent evidence from observational studies”).²

MICHAEL C ROMMEN, DO
CAROL HOWARD, MD
 IN HIS IMAGE FMR
 TULSA, OK

1. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A, et al. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev.* 2014; (7):CD006401. [STEP 1]
2. National Heart, Lung, and Blood Institute. *Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Full Report.* Chapter 9: Lipids and lipoproteins. 2012:94–140. NIH publication 12-7486. http://www.nhlbi.nih.gov/files/docs/guidelines/peds_guidelines_full.pdf. Published October 2012. Accessed May 26, 2017. [STEP 3]

What are effective interventions for chronic or recurrent yeast vaginitis?

EVIDENCE-BASED ANSWER

Induction of clinical remission with oral fluconazole followed by once-weekly suppressive therapy for 6 months decreases recurrence of yeast vaginitis during suppression by 19% (number needed to treat [NNT]=6) compared with placebo (SOR: **A**, meta-analysis of RCTs). Intravaginal nystatin for 14 days monthly for 6 months is as effective as once-weekly oral fluconazole suppression, but is more effective in cases caused by *Candida glabrata* (SOR: **B**, single RCT). When measuring short-term (1 month) outcomes in patients with recurrent disease, boric acid suppositories are more effective than nystatin, but similar to fluconazole. In the subset of cases caused by *C. glabrata*, boric acid is more likely to be effective than fluconazole (SOR: **B**, systematic review not limited to RCTs).

A meta-analysis of 2 double-blind RCTs evaluated the efficacy of weekly fluconazole for 6 months in 407 women (mean age 33 years) with recurrent vulvovaginal candidiasis.¹ Participants received 3 doses of 150 mg fluconazole orally at 3-day intervals to induce remission and then were randomized to receive 150 mg oral fluconazole or placebo weekly for 6 months. Inclusion criteria were nonpregnant women, 4 or more mycologically proven episodes of yeast vaginitis within 12 months, no history of antifungal use in past 4 weeks, and no history of diabetes mellitus or HIV infection.

Fewer women experienced a clinical recurrence in the fluconazole group than the placebo group immediately after treatment (12% vs 64%; odds ratio [OR] 0.10; 95% CI, 0.03–0.34; NNT=2), at 3 months after treatment (36% vs 73%; OR 0.23, 95% CI, 0.07–0.74; NNT=3), and at 6 months after treatment (61% vs 80%; OR 0.39, 95% CI, 0.24–0.64; NNT=6).¹

An unblinded RCT (N=296, mean age 30 years, range 18–44 years) compared vaginal nystatin suppositories with oral fluconazole treatment for efficacy and safety.² Recurrent vulvovaginal candidiasis was defined similar to the study above. The exclusion criteria were pregnancy, sexually transmitted diseases, gynecological abnormality requiring treatment, antifungal use in the week before enrollment, or

infection with more than 1 *Candida* species. Patients were randomized to nystatin 20 MU vaginal suppository daily for 14 days followed by 20 MU daily for 7 days before and after menstruation each month or oral fluconazole 150 mg on days 1, 4, and 7 followed by 150 mg weekly for 6 months.

At 6 months, no significant difference was noted in women who were mycologically free of infection in the nystatin group (81%) compared with the fluconazole group (70%; $P>.05$), as well as 6 months after that (81% and 82%, respectively; $P>.05$). However, the cure rate in the 58 patients with *C. glabrata* was 64% in the nystatin group and 12% in the fluconazole group (statistical significance not reported).²

A 2011 systematic review of 14 studies (2 RCTs, 8 case series, and 4 case reports) evaluated intravaginal boric acid for recurrent vulvovaginal candidiasis in women 16 to 70 years old.³ Results were not pooled, but were reported separately. Both RCTs compared boric acid 600 mg vaginal suppository once daily for 2 weeks with either fluconazole 150 mg orally once (15 day follow-up) or nystatin 100,000 U daily for 14 days (1 month follow-up).

Boric acid resulted in better mycologic cure rates than nystatin (92% vs 64%, respectively; $P=.0001$). Although no difference was noted in overall mycologic cure rates between boric acid and fluconazole, boric acid resulted in higher cure rates in the subset of women with *C. glabrata* (64% vs 29%, respectively; $P=.005$).³

FEREMUSU KAMARA, MD
OLUSESAN OLOTU, MD
ABIODUN OTOLORIN, MD
RYAN RABILALL, MD
 HOWARD UNIVERSITY FMR
 WASHINGTON, DC

1. Rosa MI, Silva BR, Pires PS, Silva FR, Silva NC, Silva FR, et al. Weekly fluconazole therapy for recurrent vulvovaginal candidiasis: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol.* 2013; 167(2):132–136. [STEP 1]
2. Fan S, Liu X, Wu C, Xu L, Li J. Vaginal nystatin versus oral fluconazole for the treatment for recurrent vulvovaginal candidiasis. *Mycopathologia.* 2015; 179(1-2):95–101. [STEP 2]
3. Iavazzo C, Gkegkes ID, Zarkada IM, Falagas ME. Boric acid for recurrent vulvovaginal candidiasis: the clinical evidence. *J Womens Health (Larchmt).* 2011; 20(8):1245–1255. [STEP 1]

Interested in submitting a letter to the editor?

Visit www.fpin.org/letters or email ebp@fpin.org for more information.

In geriatric adults with newly diagnosed dementia, does psychoeducation for their caregivers decrease caregiver burden or result in clinical improvement in the patient's dementia?

EVIDENCE-BASED ANSWER

Dementia psychoeducation delivered to the caregivers of persons with newly diagnosed dementia decreases caregiver burden and improves their sense of well-being when taught by a trained medical professional. However, this enhanced sense of well-being or decreased burden does not directly translate into improved caregiver quality of life (QOL). No evidence could be found in the literature to suggest any clinical improvement in the patient's dementia severity, or rate of nursing home placement (SOR: **A**, systematic review of RCTs).

A 2015 systematic review of 5 RCTs (N=395) examined the effect of dementia educational programs on caregiver's perceived burden, as measured by the Zarit Burden scale.¹ The scale is based on the cumulative addition of scores for 22 statements related to burden, with options from 0 (never) to 4 (nearly always). Each of the 5 studies' interventions focused on the caregiver education delivering facts about dementia, discussing possible coping strategies, and developing behavior management skills.

The average caregiver burden score was 8.1 points less (95% CI, 4.1–12.3) for caregivers receiving an intervention versus usual care. A limitation of the studies was their heterogeneity in the types of dementia education provided, including in-home intervention, work-shops/classes, or phone call support. However, the study authors did account for the heterogeneity by including trials carrying low to moderate risk of bias and excluding other trials that were more dissimilar from the 5 pooled trials.¹

In 2015, a prospective RCT evaluated the effect of psychoeducational support delivered by neurologists and social workers on caregivers of patients with dementia

living in the community, assessing rates of nursing home placement and caregiver QOL scores over 3 years.² In the study, 84 patient-caregiver dyads received a total of 16 days' engagement in counselling, education, and support groups to address dementia education as well as coping strategies, whereas 152 control dyads received only basic education about Alzheimer's dementia by a memory clinic nurse.

The difference between the rates of nursing home placement for the intervention and control groups (adjusted for mortality) were not significantly different. No significant differences were found when comparing several caregiver QOL indices.²

A 2003 RCT evaluated the effect of intensive psychoeducation delivered by an interventionist (with a master's degree in health education) on general well-being and depression in caregivers as well as effect on memory and problem behaviors in the patients with dementia.³ In the study, 82 patient-caregivers dyads were randomized to receive dementia behavior education and targeted education on stress management, while 85 dyads received behavioral care education alone. The trial was not included in the 2015 systematic review because of different scales for measuring effect.

The addition of stress management education statistically increased General Well-being scores (for caregivers vs behavior education only, 76.5 vs 67.5; $P=.045$ on a 110-point scale). No significant difference was noted between groups in caregiver depression or improvement in patients' dementia symptoms.³

AMY REINHART, MD

BACHIR TAZKARJI, MD, CCFP

TRILLIUM HEALTH PARTNERS—SUMMERVILLE FAMILY HEALTH TEAM
MISSISSAUGA, ONTARIO, CANADA

1. Jensen M, Agbata IN, Canavan M, McCarthy G. Effectiveness of educational interventions for informal caregivers of individuals with dementia residing in the community: systematic review and meta-analysis of randomised controlled trials. *Int J Geriatr Psychiatry*. 2015; 30(2):130–143. [STEP 1]
2. Koivisto AM, Hallikainen I, Välimäki T, Hongisto K, Hiltunen A, Karppi P, et al. Early psychosocial intervention does not delay institutionalization in persons with mild Alzheimer disease and has impact on neither disease progression nor caregivers' well-being: ALSOVA 3-year follow-up. *Int J Geriatr Psychiatry*. 2016; 31(3):273–283. [STEP 2]
3. Burns R, Nichols LO, Martindale-Adams J, Graney MJ, Lumms A. Primary care interventions for dementia caregivers: 2-year outcomes from the REACH study. *Gerontologist*. 2003; 43(4):547–555. [STEP 2]