ISSN 1095-4120 (print)
ISSN 2473-3717 (online)

Vol 20 | No. 10 | October 2017

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

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FPIN
Family Physicians Inquiries Network

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

Evidence-based cosmesis

As we wrapped up work on a Clinical Inquiry for FPIN recently, my resident coauthor and I found ourselves in a quandary about what strength of recommendation to use. The outcome we were looking at was weight loss and we could not decide if this endpoint was a "patient-oriented outcome that matters" or just an intermediate outcome (with unclear effect on mortality and morbidity in this research). Our problem, of course, was that weight can be both types of outcomes.

I have already seen other folks take opposite sides of this dichotomy of interpretation. We published a *HelpDesk Answer* in *EBP* a while back that also used weight as the outcome. The intervention caused patients to lose weight (at least a little) and the author gave the clinical recommendation a **B** rating. Later, a reader wrote in asserting that the rating should have been a **C** because weight loss is cosmetic, and not an important outcome in and of itself.

So what are we supposed to do with all the research about cosmetic interventions? We have creams that decrease acne (benzoyl peroxide and retinoids). We have lotions that increase crown hair growth (minoxidil). There are drops that make your eye lashes grow longer (bimatoprost) and surgeries to make your eye color lighter. Weight loss for its own sake may fall into this category of interventions.

In a Puritanical frame of mind, cosmetic outcomes are easy to pass off as vanities, not worth serious attention, and certainly not worth public healthcare funding. Give them all a **C** rating!

But looks are not inconsequential. Go ahead and rage against superficialities, but there's no denying that appearances affect how others treat you. Your social acceptance is an outcome that matters, a lot. If a study result shows that an intervention does what a patient really wants, well then, give that trial a **B** rating!

Enough editors here at *EBP* have run into this conundrum about the clinical significance of weight that we all sat down over coffee and pastry (!) recently and reached a consensus. Now a 5-pound weight loss will be considered a patient-oriented outcome that matters at FPIN.

That won't settle the debate, but at least I can finish writing my Clinical Inquiry.

Jon O. Neher, MD

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

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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.

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In asymptomatic patients, do coronary artery calcium scores predict myocardial infarction risk?

EVIDENCE-BASED ANSWER

Yes, coronary artery calcium scores (CACSs) identify patients at increased risk for outcomes such as myocardial infarction (MI) and death from coronary heart disease (CHD). However, in asymptomatic patients, due to the low pretest probability of these outcomes (<1%), a high CACS (about ≥300) has a low positive predictive value (PPV=2%–4%) over 3 to 4 years (SOR: **B**, consistent prospective cohort trials).

Evidence summary

A 2008 prospective cohort study of 6,722 patients evaluated the prognostic value of CACSs for angina and major cardiac events such as MI and death from CHD.[1] The study included participants from 4 ethnic groups–white, black, Hispanic, and Chinese–in 6 urban communities in the United States who were between 45 and 84 years of age and had no clinical cardiovascular disease at study entry. Patients were followed for a median of 3.8 years. The cardiac risk predicted by the CACS was calculated after adjusting for standard risk factors, such as family history, smoking history, level of low-density lipoprotein and high-density lipoprotein, hypertension, and diabetes.

Overall, 89 (1.3%) participants had a major cardiac event. Compared with participants who had no coronary calcium, participants with a CACS between 1 and 100 had an increased risk of a major cardiac event (hazard ratio [HR] 3.9; 95% CI, 1.7–8.8). Participants with CACSs between 101 and 300 had an even higher risk (HR 7.1; 95% CI, 3.1–17), but this risk did not continue to increase in participants with scores above 300 (HR 6.9; 95% CI, 2.9–16). Doubling of the CACS increased the risk of a major coronary event by a range of 15% in Hispanic patients to 35% in black patients.[1]

Even though CACS provides additional risk assessment, the posttest risk remained low: 3.2% of patients with a calcium score of 101 to 300 and 3.9% of patients with a calcium score of more than 300 had a major cardiac event. By comparison, 0.2% of patients with no coronary calcium had a major cardiac event. No significant difference was noted among the ethnic groups in the predictive value of calcium scores. A positive CACS, defined as a CACS of more than 300, resulted in a PPV of 4% (95% CI, 3–5).[1]

A 2005 prospective cohort study (N=10,746 adults, age range 22–96 years) free of known CHD evaluated the association between CACS and risk of cardiac events (MI and death from CHD) over a mean of 3.5 years.[2] The CACSs were divided into 4 groups (no detectable calcium; CACS 1–38 for men and 1–16 for women; CACS 39–249 for men and 17–112 for women; and CACS >250 for men and >113 for women).

Overall, 81 (0.75%) major cardiac events occurred during the study period. The age-adjusted rates of major cardiac events were significantly different among the 4 CACS groups at 0.4%, 1.5%, 4.8%, and 8.7% (P<.0001 for the trend) for men, and 0.7%, 2.3%, 3.1%, and 6.3% (P=.02 for the trend) for women. Only 2.3% (247 of 10,746) of participants in the highest calcium score group had a major cardiac event. A "positive" CACS, defined here as CACS of more than 250 for men and more than 113 for women, resulted in a PPV of 2% (95% CI, 2–3).[2] EBP

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ERRATUM (OCTOBER 2017)

In the July 2017 issue, for the Spotlight on Pharmacy article entitled, What is the most appropriate treatment for asymptomatic bacteriuria in pregnancy? [EBP 2017; 20(7):14–15], the author's program affiliation was listed incorrectly. The author, Jesse Clark, DO, is affiliated with the University of North Carolina FPRP, in Chapel Hill, NC.

We regret the error, and apologize for any confusion.

Who comes in second? The race against sulfonylureas and DPP4s as add-on therapy

Ou SM, Shih CJ, Chao PW, Chu H, Kuo SC, Lee YJ, et al. Effects on clinical outcomes of adding dipeptidyl peptidase-4 inhibitors versus sulfonylureas to metformin therapy in patients with type 2 diabetes mellitus. *Ann Intern Med*. 2015; 163(9):663–672..

A population-based cohort study with more than 70,000 patients with diabetes mellitus type 2 examined if sulfonylureas or dipeptidyl peptidase-4 (DPP-4) inhibitors are more effective when added as the second agent to metformin.

Data were obtained from the National Health Insurance program in Taiwan. This study created a propensity score-matched cohort of 10,089 pairs of patients taking sulfonylureas and DPP-4 inhibitors. After propensity scoring, no differences were noted in baseline characteristics between the groups.

Over a mean follow-up of 3.3 years, DDP-4 inhibitors had a lower risk than sulfonylureas of all-cause mortality (366 vs 488 events; hazard ratio [HR] 0.63; 95% CI, 0.55–0.72), major cardiovascular events (209 vs 282 events; HR 0.68; 95% CI, 0.55–0.83), ischemic stroke (144 vs 203 events; HR 0.64; 95% CI, 0.51–0.81), and hypoglycemia (89 vs 170 events; HR 0.43; 95% CI, 0.33–0.56). No difference was noted between the groups in risk of myocardial infarction and hospitalizations for heart failure.

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

Bottom line: When deciding which agent to add after metformin, DPP-4 inhibitors appear to provide a greater reduction in risk of death, cardiovascular events, and stroke with less hypoglycemia and no increased risk of myocardial infarction or congestive heart failure compared with sulfonylureas.

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PPIs decrease risk of upper GI bleed in patients on warfarin plus antiplatelet agents/NSAIDs

Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD, et al. Association of proton pump inhibitors with reduced risk of warfarin-related serious upper gastrointestinal bleeding. *Gastroenterology*. 2016; 151(6):1105–1112.e10

This retrospective cohort study examined rates of hospitalization for upper gastrointestinal (GI) bleeding in more than 97,000 Medicare and Medicaid patients taking warfarin with and without proton pump inhibitor (PPI) co-therapy (>75,000 person-years of follow-up). Researchers also evaluated concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) or antiplatelet agents.

Compared with patients taking warfarin alone, patients taking warfarin plus a PPI had more baseline risk factors for upper GI bleeding such as a history of a GI bleed, cardiovascular comorbidities, or liver disease. For patients receiving both warfarin and an antiplatelet/NSAID, PPI co-therapy reduced the risk of hospitalization for upper GI bleeding (adjusted hazard ratio [aHR] 0.55; 95% CI, 0.39–0.77), and resulted in a reduction of 128 hospitalizations per 10,000 person-years (95% CI, –66 to –173).

No difference was noted in risk among the various antiplatelet drugs or NSAIDs. However, for patients taking warfarin but not an antiplatelet/NSAID, PPI co-therapy did not significantly decrease the risk of hospitalization for upper GI bleeding (HR 0.86; 95% CI, 0.70–1.06). This study may be underpowered to detect smaller but clinically significant reductions in upper GI bleed risk for these patients.

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

Bottom line: In patients taking warfarin plus an antiplatelet agent or NSAID, PPI co-therapy decreases the risk of hospitalization due to upper GI bleed. EBP

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Additional information regarding the PURLs and Diving for PURLs series can be found at: **http://fpin.org/page/WhatarePURLs**

In pediatric, suicidal, and other high-risk patients, does screening for access to guns and a brief office intervention improve gun safety practices?

CASE

A 13-year-old African American boy presents to clinic for a sports physical. He is thriving in school; does not use tobacco, alcohol, or drugs; and is not yet sexually active. He lives with his 2 sisters and his mother, who struggles with mental illness. His mother's concern is that he was seen handling a firearm with some of his friends. What more should you say or do about the firearm issue?

Evidence-based answer

Screening for firearms in the home followed by counseling to promote safe gun storage may improve storage practices. Provision of a safe storage device increases the likelihood of safe gun storage behaviors.

Evidence summary

According to the Centers for Disease Control and Prevention, 84,997 nonfatal and 36,252 fatal injuries occurred from the discharge of firearms in the United States in 2015, the year for which the latest data are available.[1] Children 18 years old and younger sustained 2,876 of these injuries and 2,080 of these deaths. In children younger than the age of 15, a total of 443 deaths were caused by firearms.

As many as one-third of children live in a home with at least 1 gun; half of these weapons are unlocked or loaded in their homes.[2] The following reviews explore whether screening by physicians and brief interventions promote the safety of gun storage with the use of cable locks, storing the gun unloaded, and storing the ammunition separately from the guns.

In a 2016 systematic review that analyzed 7 studies (N=4,858), families who had at least 1 gun in the home were provided counseling, counseling plus a free safety device (cable lock or gun safe), or a safety device alone.[3]

In the studies that provided a safety device (1 quasi-experimental design and 2 RCTs), a significant increase in safe storage practices was noted (quasi-experimental: risk ratio [RR] 2.3; 95% CI, 1.5–3.4; RCT 1: risk difference [RD] 22%; *P*<.001; RCT 2: 35% of homes in the intervention group and 89% of those in the control group reported having any guns unlocked at follow-up, *P*<.001). Due to heterogeneity of the studies, a composite statistical analysis could not be performed.

Of the studies that did not include a safety device, 1 quasi-experimental study had a positive effect on safe storage practices. Both studies that provided counseling (one with and the second without a voucher for a safety device) did not show an effect (with voucher: RD 6.3%; 95% CI, –1.3 to 17.2; without voucher: odds ratio [OR] 1.2; 95% CI, 0.9–1.7). A broad media campaign also failed to show improvement in safe storage practices. Again, the authors were unable to pool the data into a meta-analysis due to the heterogeneity of the studies.[3]

Another 2016 systematic review analyzed physicians' attitudes and screening practices in addition to interventions to reduce firearm-related injuries.[4] Of the 12 studies (N=7,931) directed at effectiveness of interventions, the 2 highest quality studies showed improvement in gun safety measures, including safe storage in the homes of pediatric patients (OR 2.0; 95% CI not reported; *P*=.001) and a decrease in gun carry in a high-risk teen population (RR 0.31; 95% CI, 0.11–0.90).[4] Four low- to moderate-quality RCTs failed to show improvement in gun safety, perhaps because of significant methodological concerns including low follow-up and enrollment bias. The 6 remaining studies were a mix of quasi-experimental and retrospective cohort studies. Most of the studies were small sample sizes and underpowered. All studies relied on self-report to determine change in storage behaviors. The authors concluded that screening and interventions may increase rates of safe storage in high-risk populations, including pediatric patients, suicidal patients, and high-risk youth.[4]

CASE WRAP-UP

With further questioning, you discover that your patient does not have a firearm in the home and his mother would not allow one. You and the patient negotiate that he will not handle any guns without the direct supervision of an adult in a controlled setting. EBP

CONTINUED ON PAGE 14

Low-carbohydrate diet or low-fat diet, which is better for weight loss?

EVIDENCE-BASED ANSWER

Patients on very-low-carbohydrate ketogenic diets (<60 g/d carbohydrates or <10% of calories) achieve about 1 to 2 kg more weight loss over 6 to 12 months compared with patients on low-fat diets. Less carbohydrate restriction (<225 g/d or <45% of calories) is not consistently better than a low-fat diet (SOR: **A**, meta-analyses of RCTs).

A 2013 systematic review and meta-analysis of 13 RCTs (N=1,415) compared weight loss in patients assigned to very-low-carbohydrate ketogenic diets (<50 g/d carbohydrates or 10% of daily energy from carbohydrates) or low-fat diets (low calorie with <30% calories each day from fats) over at least a 12-month period.[1] Included RCTs enrolled patients older than age 18 with mean body mass index of more than 27.5 kg/m^2. Studies were excluded if they involved pharmacological interventions or were duplicate publications of other included trials.

In 13 trials (12–24 months' duration), weight loss in the ketogenic diet group (n=712) ranged from 0 to 13 kg and in the low-fat diet group (n=703) ranged from 0.2 to 12 kg. The ketogenic diet group had more mean weight loss than the low-fat diet group (weighted mean difference [WMD] –0.91 kg; 95% CI, –1.7 to –0.17). Limitations included high dropout rate (4 of 13 trials with >50% dropout rates) and poor adherence to prescribed carbohydrate restriction.[1]

A 2012 systematic review and meta-analysis of 23 RCTs (N=2,788) compared the effects of low-carbohydrate diets (<45% calories from carbohydrates or <225 g/d carbohydrates) versus low-fat diets (<30% calories from fat) on weight loss in overweight and obese adults.[2] This meta-analysis included 11 RCTs from the meta-analysis above, but also included trials with less carbohydrate restriction and trials of shorter duration (≥6 months). Exclusion criteria included nonrandom treatment allocation, no difference in carbohydrate or fat intake between the groups, or differences in other macronutrient and energy intake between the groups.

After diet intervention for an average of 12.6 months, weight loss in the low-carbohydrate group (n=1,392) was 6.1 kg compared with a weight loss of 5.0 kg in the low-fat group (n=1,396), a nonsignificant difference (23 trials, n=2,788; WMD 1.0 kg; 95% CI, –0.2 to 2.2). After adjustment for possible publication bias, the difference became significant, favoring the low-carbohydrate diet group (WMD 3.2 kg; 95% CI, 2.0–4.5).[2]

In a subgroup analysis of 21 trials (n=not reported), patients in a highly restricted low-carbohydrate group (<60 g/d carbohydrates) had greater weight loss than patients on a low-fat diet (WMD 2.0 kg; 95% CI, 0.6–3.4). In 15 trials (n=not reported), patients with low-carbohydrate diet adherence for more than 1 year had more weight loss than patients on a low-fat diet (WMD 0.9 kg; 95% CI, 0.3–1.6). Limitations included unclear trial quality, heterogeneity of included trials, and publication bias.[2]

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Does morning or evening administration of long-acting insulin affect glycemic control in patients with type 2 diabetes?

EVIDENCE-BASED ANSWER

The timing of long-acting insulin injection has no difference on fasting blood glucose reductions or pharmacokinetics (SOR: **C**, RCTs with disease-orientated outcomes). However, evening administration leads to fewer patients experiencing symptomatic hypoglycemia than morning administration, with no difference in total hypoglycemic or nocturnal hypoglycemic events (SOR: **B**, single RCT).

In 2005, a 24-week multinational, open-label, randomized trial evaluated the frequency of nocturnal hypoglycemia episodes, and glycosylated hemoglobin (HbA1C) and fasting blood glucose (FBG) levels after morning or bedtime administration of insulin glargine plus glimepiride at doses of

2, 3, or 4 mg.[1] Patients with type 2 diabetes mellitus (N=624) poorly controlled on oral agents were randomized to either morning or bedtime insulin glargine, with the dose titrated to achieve FBG levels of no more than 100 mg/dL.

After 24 weeks, mean doses of insulin glargine were similar: 35 units in the morning and 32 units at bedtime (*P*=.15). FBG reductions (–77 vs –81 mg/dL; *P*=.08) and frequency of nocturnal hypoglycemia (13% vs 15%; 95% CI, –100% to 2.8%) were similar for morning and evening administration. At the end of 24 weeks, no difference was noted between the morning and evening insulin groups for the percentage of patients with HbA1C levels less than 7.0% (48% vs 47%; *P*=.66) or reduction in HbA1C from baseline (1.7% vs 1.6%; *P* not significant). Limitations of this trial included its open-label design, varying dosages of glimepiride, and no mention of whether the hypoglycemic episodes were symptomatic.[1]

A 2003 open-label RCT investigated the safety and efficacy of 3 mg glimepiride combined with either morning or bedtime insulin glargine or bedtime neutral protamine (NPH) insulin in 695 patients with type 2 diabetes over 24 weeks.[2] Insulin was titrated to achieve FBG levels of 100 mg/dL or more. Outcomes included HbA1C, blood glucose levels, and episodes of hypoglycemia.

After 24 weeks, the mean dose of insulin glargine was 40 units in the morning and 39 units at bedtime. Morning insulin glargine compared with bedtime insulin glargine resulted in a slightly greater improvement in HbA1C from baseline (–1.2% vs –0.96%; *P*=.008) and more patients reaching HbA1C levels of 7.5% or less (43% vs 33%; *P*=.02). No difference was noted in FBG reductions from baseline between morning and evening insulin administration (–92 vs –94 mg/dL; *P*=.2).[2]

More patients taking insulin glargine in the morning versus bedtime had symptomatic episodes of hypoglycemia (56% vs 43%; *P*=.004). No difference was noted in overall episodes of hypoglycemia (74% vs 68%; *P*>.2) or nocturnal hypoglycemia (17% vs 23%; *P* not reported) between morning and bedtime dosing of insulin glargine. This trial was limited by its open-label design.[2]

A 2015 randomized, single-dose, open-label trial evaluated the pharmacokinetics and pharmacodynamics of morning versus evening dosing of insulin glargine (0.4 units/kg) in 10 diabetic patients using a 24-hour euglycemic glucose clamp technique.[3] Researchers gave patients a continuous intravenous glucose infusion to maintain plasma glucose at 100±5 mg/dL for 24 hours. Administration of insulin glargine occurred at either 1,000 or 2,200 hours and insulin activity, defined as the change in the rate of exogenous glucose infusion, was measured.

No statistically significant difference was observed between the morning and evening glargine groups in insulin activity as measured by the 24-hour glucose infusion rate area under the curve.[3]

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When should patients presenting with CVA receive thrombolytic agents?

EVIDENCE-BASED ANSWER

Thrombolytic therapy improves the outcomes of neurological deficits in patients presenting with an ischemic stroke when given within 3 to 4.5 hours of symptom onset. Patients do not benefit from thrombolytic agents given later (SOR: **A**, meta-analysis).

In 2015, a systematic review evaluating 68 studies (N=108,082) of acute stroke treatment included RCTs, review articles, guideline statements, and observational studies.[1] A meta-analysis of 8 placebo-controlled RCTs of intravenous (IV) recombinant tissue plasminogen activator (rtPA) involving 2,775 patients confirmed the importance of timing of thrombolytic therapy by the following adjusted odds ratios (ORs) of good outcome by time from symptom onset to treatment: 2.55 (95% CI, 1.44–4.52) for 0 to 90 minutes, 1.64 (95% CI, 1.12–2.40) for 91 to 180 minutes, and 1.34 (95% CI, 1.06–1.68) for 181 to 270 minutes. A good outcome was defined as a modified Rankin score of 0 to 1 at 3 months. (Modified Rankin scores run from 0 for no stroke symptoms to

6, signifying death.) Patients receiving IV rtPA more than 4.5 hours after symptom onset had no net benefit.

A 2014 meta-analysis evaluated 27 RCTs (3 trials were included in the meta-analysis above) involving 10,187 patients who were treated up to 6 hours after the onset of symptoms of cerebral vascular accidents (CVAs) from definite ischemic strokes.[2] Overall, 16% of participants were older than 80 years. Four trials used intraarterial administration of urokinase or pro-urokinase, while the rest used IV routes for a variety of thrombolytic agents. About 70% of participants received rtPA, and most patients had moderate to severe strokes.

Five trials were single-blind without a placebo. In 1 trial, the initial 10% of patients were placebo controlled, while the remainder received treatment only. In the remaining 21 studies, treatment was placebo controlled.[2]

Thrombolytic therapy administered up to 6 hours after CVA significantly reduced mortality and dependency (modified Rankin scores of 3–6) at 3 to 6 months after the stroke (22 trials, n=9,318; OR 0.85; 95% CI, 0.78–0.93). However, therapy increased the risk of a symptomatic intracranial hemorrhage (27 trials, n=10,186; OR 3.75; 95% CI, 3.11–4.51) and early death (13 trials, n=7,458; OR 1.69; 95% CI, 1.44–1.98). Early death after thrombolysis was mostly attributable to intracranial hemorrhage. Death by 3 to 6 months after the stroke was also increased by therapy (27 trials, n=10,187; OR 1.18; 95% CI, 1.06–1.30). Treatment within 3 hours of stroke symptom onset was more effective in reducing death or dependency (10 trials, n=2,160; OR 0.66; 95% CI, 0.56–0.79) without an increase in death (11 trials, n=2,187; OR 0.99; 95% CI, 0.82–1.21). Patients older and younger than 80 years benefitted equally from treatment. The reviewers rated the overall quality of the evidence as good.[2]

The American Heart Association and American Stroke Association Guidelines for the Early Management of Patients with Acute Ischemic Stroke 2015 recommended the use of IV thrombolytic agents for up to 4.5 hours of the onset of ischemic stroke symptoms.[1]

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Does long-term use of proton pump inhibitors cause vitamin B_{12} deficiency?

EVIDENCE-BASED ANSWER

Vitamin B_{12} deficiency is associated with either long-term proton pump inhibitor (PPI) or histamine-2 receptor blocker (H2 blocker) use, but a causal relationship is not established (SOR: **B**, meta-analysis of high-quality case-control studies).

A 2015 systematic review and meta-analysis of 4 high-quality case-control studies and 1 observational study (N=23,607; age ≥18 years) evaluated vitamin B_{12} levels in patients taking acid-lowering agents for 12 to 60 months.[1] These studies covered a 14-year period from 2000 to 2014. Acid-lowering agents were defined as either PPIs or H2 blockers. The diagnosis of vitamin B_{12} deficiency was defined as vitamin B_{12} levels less than 150 pg/mL, vitamin B_{12} levels of 130 to 300 pg/mL with elevated methylmalonic acid (>271 nmol/L) and homocysteine (>13.9 mol/L), or patients receiving intramuscular vitamin B_{12} replacement.

At baseline, 4,379 patients taking acid-lowering agents had vitamin B_{12} deficiency. The analysis demonstrated an association between long-term acid-lowering medication use and vitamin B_{12} deficiency (hazard ratio [HR] 1.8; 95% CI, 1.4–2.5). The authors pointed out that association does not prove causation.

A 2013 retrospective case-control study examined the association of vitamin B_{12} deficiency with the use of PPIs or H2 blockers for 2 years or more.[2] The 25,956 case patients were at least 18 years old and incidentally diagnosed with vitamin B_{12} deficiency. They were matched with 184,199 control patients who did not have vitamin B_{12} deficiency. This study was included in the 2015 meta-analysis noted above, but is by far the largest study in the meta-analysis and, additionally, it reports on PPI and H2 blocker use separately.

Use of PPIs or H2 blockers in the case and control populations was determined by dispensed medication data. The diagnosis of vitamin B_{12} deficiency was determined by diagnosis code of pernicious anemia, diagnosis code of other vitamin B_{12} deficiency, laboratory record of a low serum vitamin B_{12} level, or receipt of at least 6 months of vitamin B_{12} supplementation, all from January 1997 to June 2011.[2]

Of the case patients, 12% were prescribed a PPI and 4.2% an H2 blocker for 2 years or more compared with 7.2% and 3.2%, respectively, in the control group. A statistically significant association was noted with vitamin B_{12} deficiency for both PPI use (odds ratio [OR] 1.7; 95% CI, 1.6–1.7) and H2 blocker use (OR 1.3; 95% CI, 1.2–1.3). The association between PPI use and vitamin B_{12} deficiency decreased after PPI use was discontinued; OR was 1.8 (95% CI, 1.5–2.0) if the last prescription was dated within 1 year compared with an OR of 1.4 (95% CI, 1.1–1.7) if the last prescription was dated 3 or more years ago. The study was of good quality with a large sample size (n=210,155) that represented the general population of the region within a large integrated healthcare system.[2]

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What are the most effective pharmacologic treatments for adults with chronic primary insomnia?

EVIDENCE-BASED ANSWER

Benzodiazepines (particularly triazolam for 1 week) and nonbenzodiazepine hypnotic agents (particularly zolpidem and zopiclone for 2–5 weeks) modestly improve sleep-onset latency and subjective sleep reporting (SOR: **B**, meta-analysis of RCTs with publication bias and heterogeneity). Ramelteon does not improve sleep-onset latency or subjective sleep reporting to a clinically significant extent (SOR: **B**, meta-analysis of low quality RCTs).

The 2014 International Classification of Sleep Disorders defined chronic insomnia as symptoms of insomnia persisting 3 times a week for 3 months.[1] The DSM-V criteria for diagnosing insomnia includes difficulty sleeping at least 3 nights per week that is present for at least 3 months.[2]

A 2007 meta-analysis of 105 RCTs examined the use of benzodiazepines (52 RCTs, N=5,582), non-benzodiazepine hypnotics (45 RCTs, n=10,926), and antidepressants (8 RCTs, n=873) for the treatment of chronic insomnia.[3] Chronic insomnia was defined as presence of a disturbance in sleep initiation or maintenance problem lasting at least 4 weeks, or history of persistent sleep disturbance, or attendance to a sleep disorders clinic. Most benzodiazepine trials lasted less than 1 week and used triazolam 0.125 to 0.5 mg. Some studies combined benzodiazepine and nonbenzodiazepine therapy. Zolpidem 10 to 15 mg and zopiclone 2.5 to 15 mg were the most common therapies used in the nonbenzodiazepine trials, typically administered for 2 to 5 weeks. Antidepressants were administered from 1 night to 4 weeks and included doxepin, trazodone, pivagabine, or trimipramine.

Objective evaluation by polysomnography demonstrated statistically significant but clinically insignificant shortening of sleep-onset latency in all 3 classes of medications (nonbenzodiazepines –13 min, 95% CI, –17 to –8.8; benzodiazepines –10 min, 95% CI, –17 to –3.4; antidepressants –7.0 min, 95% CI, –11 to –3.3). Subjective evaluation of sleep-onset latency using sleep diaries found greater improvement with benzodiazepines (–20 min; 95% CI, –24 to –15) than nonbenzodiazepines (–17 min; 95% CI, –20 to –14) or antidepressants (–12 min; 95% CI, –22 to –2.2). Limitations included a strong publication bias in studies of benzodiazepines and nonbenzodiazepines and the relative lack of antidepressant studies. Many included studies did not use a standard definition of insomnia.[3]

A 2014 systematic review and meta-analysis examined 13 placebo-controlled RCTs (crossover and parallel studies) of ramelteon 4 to 32 mg, a selective melatonin receptor agonist, for the treatment of insomnia in adults (N=5,812).[4] Specific criteria for chronic insomnia were not distinguished in this review. The mean duration of the included studies was 38 days. The primary outcome was sleep latency evaluated with polysomnography and subjective patient report.

Use of ramelteon demonstrated clinically insignificant improvement in subjective sleep latency (–4.6 min; 95% CI, –7.2 to –2.0) and sleep-onset latency by polysomnography (–9.4 min; 95% CI, –12 to –6.4). The methodology and

duration of sleep studies were not reported in many of the RCTs included in this meta-analysis.[4]

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

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How accurate are patient-collected vaginal gonorrhea and chlamydia swabs in detecting infection?

EVIDENCE-BASED ANSWER

Patient-collected vaginal swabs are accurate—with a sensitivity of 92% and a specificity of 98% for chlamydia and a sensitivity of 98% and a specificity of 97% for gonorrhea, when using provider-collected endocervical swabs as the gold standard (SOR: **B**, meta-analysis of cross-sectional studies).

A 2015 meta-analysis included 21 trials with 7 cross-sectional studies that specifically compared the accuracy of patient-collected vaginal swabs with provider-collected endocervical swabs in the detection of chlamydia and gonorrhea in women (N=2,115).[1] Inclusion criteria for the meta-analysis required that provider-collected swabs served as the reference standard and nucleic acid amplification testing was used to detect both positive and negative results. In all 7 cross-sectional studies, both patient and provider swabs were collected during a single clinic visit.

The pooled sensitivity of patient swabs from the 6 studies testing for chlamydia was 92% (95% CI, 87–95) and the specificity was 98% (95% CI, 97–99). The reported prevalence of chlamydia for each study ranged from 3% to 16%. In the lone study detecting gonorrhea, patient-collected swabs had a sensitivity of 98% (95% CI, 88–100) and a specificity of 97% (95% CI, 94–99). Prevalence of gonorrhea in the study population was 12.6%.[1]

A cross-sectional study in 2002 compared 5 sample collection methods including first void urine samples, patient-collected vaginal swabs, self-collected tampon specimen, provider-collected endocervical swabs, and provider-collected high vaginal swabs for gonorrhea and chlamydia among 318 women attending annual pelvic examinations at a single clinic in Australia.[2] This study was excluded from the meta-analysis above because of the relatively low number of participants (N=318) and the study's definition of true-positive results. Any patient undergoing a pelvic examination was offered enrollment whether or not they were symptomatic. Patients were considered positive if any 2 collection methods were positive. Prevalence of chlamydia and gonorrhea in this population was 12%.

For chlamydia, self-collected vaginal swabs had a sensitivity of 85% (95% CI, 69–93) compared with provider-collected endocervical swabs, which had a sensitivity of 92% (95% CI, 75–97). For gonorrhea, patient-collected swabs had a sensitivity of 72% (95% CI, 53–86) compared with provider-collected swabs with a sensitivity of 93% (95% CI, 76–99). While provider-collected samples were more sensitive than patient-collected samples, the difference was not statistically significant.[2]

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What is the best first-line antibiotic for uncomplicated UTI in women?

EVIDENCE-BASED ANSWER

Nitrofurantoin, trimethoprim/sulfamethoxazole (TMP-SMX), and fluoroquinolone antibiotics are essentially of equivalent efficacy (SOR: **A**, meta-analyses of RCTs) for uncomplicated cystitis in women. Nitrofurantoin has few adverse events and minimal resistance currently and is recommended as a first-line antibiotic (SOR: **C**, expert opinion).

A 2012 network meta-analysis examined 10 RCTs (with 5,514 female patients, age ≥12 years) to find the best treatment for uncomplicated urinary tract infection (UTI), diagnosed by UTI symptoms or positive baseline culture.[1] Antibiotics included ciprofloxacin, norfloxacin, nitrofurantoin, amoxicillin-clavulanate, gatifloxacin, TMP-SMX, and fosfomycin, all given for 3 to 7 days. Short-term (1 week) and long-term (1 month) clinical and bacteriological cure (not defined) plus unspecified adverse effects were assessed. Cultures were considered positive within a range of 10^3 to 10^5 CFU/mL of an uropathogen. The studies did not directly compare each antibiotic with all others, but the authors performed a network meta-analysis to compare antibiotics using ciprofloxacin as a reference.

For short-term and long-term clinical cure, amoxicillin-clavulanate was the only antibiotic less effective than ciprofloxacin (see **TABLE**). No differences were noted in short-term or long-term clinical cure among the other antibiotics and ciprofloxacin, although nitrofurantoin and TMP/SMX did have less short-term bacteriological cure.[1]

A 2010 systematic review of 21 RCTs with 6,016 female patients 16 to 65 years old evaluated the effectiveness of various antibiotics for acute uncomplicated UTIs with several studies in common with the meta-analysis above.[2] Uncomplicated UTI was defined as symptoms of dysuria and urinary frequency, without fever or flank pain.

Study antibiotics included TMP-SMX (160/800 mg BID), nitrofurantoin (100 mg four times a day), fluoroquinolones,

TABLE

Odds ratio (95% CI) of clinical and bacteriological cure and adverse events of various antibiotics relative to the reference treatment (ciprofloxacin)[1]

	Ciprofloxacin[a]	Amoxicillin–clavulanate	Fosfomycin	Gatifloxacin	Nitrofurantoin	Norfloxacin	TMP-SMX
1 week clinic cure	1.0	0.07[b] (0.02–0.24)	—	0.93 (0.68–1.3)	0.86 (0.31–2.3)	0.63 (0.29–1.4)	0.71 (0.34–1.5)
1 week bacteriological cure	1.0	0.17[b] (0.08–0.35)	0.12 (0.03–0.42)	1.1 (0.79–1.4)	0.27[b] (0.11–0.66)	0.81 (0.35–1.9)	0.36[b] (0.18–0.72)
1 month clinical cure	1.0	0.31[b] (0.19-0.53)	—	0.93 (0.71-1.2)	1.3 (0.49-3.3)	0.91 (0.44-1.9)	0.87 (0.40-1.9)
1 month bacteriological cure	1.0	—	—	0.96 (0.75–1.2)	—	0.86 (0.42–1.8)	0.87 (0.40–1.9)
Adverse events	1.0	1.6 (0.92–2.6)	—	1.2 (0.90–1.5)	1.1 (0.41–2.8)	1.5 (0.54–4.3)	1.4 (0.60–3.4)
Dosing	200–2,000 mg × 3 days	1,000/250 mg × 3 days	3 g × 1 day	200–400 mg × 1–3 day	200–400 mg × 3–7 days	800 mg × 3–7 days	160/800 mg × 3–7 days

[a]Reference treatment.

[b]Results are statistically significant; odds ratio <1 indicates less cure or fewer adverse events.

TMP-SMX=trimethoprim/sulfamethoxazole..

and beta-lactams (cefadroxil, cefpodoxime, cefuroxime); therapies ranged from 3 to 10 days. Short-term (2 weeks) and long-term (8 weeks) symptomatic and bacteriological cure were assessed.[2]

Fluoroquinolones demonstrated greater efficacy than beta-lactams for short-term bacteriological cure; all other antibiotics had similar efficacy.[2]

In 2011, the Infectious Diseases Society of America and European Society for Microbiology and Infectious Diseases reviewed 28 randomized and open-label clinical trials to update clinical practice guidelines for the optimal treatment of uncomplicated cystitis in adult females.[3] Expert opinion was included in final recommendations.

The guidelines recommended nitrofurantoin 100 mg BID for 5 days because of minimal resistance and similar efficacy comparable to TMP-SMX (quality of evidence: A-I; good evidence to support recommendation based on >1 randomized control study). TMP-SMX 160/800 mg, 1 double-strength tablet BID for 3 days had equivalent efficacy if the infecting strain is known to be susceptible (A-I).[3]

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***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 mindfulness training an effective means of increasing physician wellness and decreasing burnout?

EVIDENCE-BASED ANSWER

Yes. Mindfulness training is associated with decreases in self-reported emotional exhaustion, depersonalization, tension, anxiety, fatigue, and inertia (SOR: **B**, prospective cohort).

In 2014, a pragmatic RCT with preintervention and postintervention measurements examined the effect of an 8-week mindfulness psychoeducational program on self-reported measures of burnout, mood, empathy, and mindfulness.[1] Participants were 68 primary healthcare professionals in Spain (23 physicians, 17 nurses, and 3 other in the intervention group vs 18 physicians, 6 nurses, and 1 other in the control group.). Outcome measures were the Maslach Burnout Inventory (MBI), Profile of Mood States (POMS), Jefferson Scale of Physician Empathy (JSPE), and Five Facets of Mindfulness Questionnaire (FFMQ).

At the program conclusion, the group receiving the intervention showed significant improvement in total MBI score and in subscales of emotional exhaustion and depersonalization, as measured by mean difference between changes in each group and standardized effect sizes. Changes in POMS self-ratings favored the intervention group for total mood disturbance as well as for the subscales of tension-anxiety and fatigue-inertia. Similarly, the intervention group demonstrated relatively greater improvement in measures of empathy (JSPE) for both total score and for the subscale of standing in the patient shoes. FFMQ changes also demonstrated greater improvement in the intervention group for total score and for subscales of observing, acting with awareness, and nonreactivity (see **TABLE**).[1]

A single-sample, pre-post mindfulness intervention in 2009 examined the effect of a continuing medical education program on self-reported measures of personal well-being, mood, and personality traits relevant to patient care.[2] Course content consisted of brief didactic material, formal mindfulness meditation, narrative and appreciative inquiry exercises, and discussion. Participants were 70 primary care physicians in Rochester, New York, who completed a course

TABLE

Outcomes from a mindfulness education program on provider wellness and burnout[1]

Outcome measure (no. items in scale, score range)	Mean group difference (95% CI)	*P* value	Standardized effect size
Maslach Burnout Inventory (MBI)			
Total group (20 items, range 0–140)	–8.0 (–13 to –0.6)	<.05	0.74
Emotional exhaustion (8 items, range 0–56)	–6.2 (–10.2 to –2.3)	<.01	1.05
Depersonalization (5 items, range 0–35)	–2.5 (–4.8 to –0.3)	<.05	0.65
Personal accomplishment (7 items, range 0–49)	1.8 (–0.5 to 4.1)	NR	0.52
Profile of Mood Scale (POMS)			
Total group (15 items, range 0–60)	–7.1 (–11 to –3)	<.001	1.15
Tension-anxiety[a]	–1.9 (–3.0 to –0.7)	<.001	1.07
Depression-dejection[a]	–2.0 (–2.1 to 0.16)	NR	0.56
Anxiety-hostility[a]	–2.0 (–2.2 to 0.3)	NR	0.49
Vigor-activity[a]	0.7 (–0.3 to 1.7)	NR	0.50
Fatigue-inertia[a]	–2.6 (–4.0 to –1.1)	<.01	1.00
Jefferson Scale of Physician Empathy (JSPE)			
Total (20 items, range 0–140)	5.2 (0.2 to 10.3)	<.05	0.71
Perspective-taking (10 items, range 0–70)	1.4 (–1.5 to 4.3)	NR	0.26
Compassionate care (8 items, range 0–56)	2.3 (–0.2 to 4.8)	NR	0.55
Standing in the patient's shoes (2 items, range 0–14)	1.5 (0.4 to 2.6)	<.05	0.55
Five Facet Mindfulness Questionnaire (FFMQ)			
Total (39 items, range 39–195)	11 (3 to 19)	<.01	0.90
Observing (8 items, range 0–40)	4.7 (1.9 to 7.3)	<.01	1.32
Describing (8 items, range 0–40)	0.6 (–1.1 to 2.2)	NR	0.29
Acting with awareness (8 items, range 0–40)	2.7 (0.2 to 5.3)	<.05	0.74
Nonjudging (8 items, range 0–40)	2.4 (–0.3 to 5.1)	NR	0.61
Nonreactivity (7 items, range 0–35)	1.8 (0.1 to 3.5)	<.05	0.64

Standardized effect size: positive values represent improvement. Values of 0.2 to 0.5 represent small changes, 0.5 to 0.8 moderate changes, and >0.8 large changes.

[a]Profile of Mood Scale subscale information not provided.

NR=not reported.

consisting of an 8-week intensive phase (2.5 hours per week plus a 7-hour retreat) and a 10-month maintenance phase of 2.5 hours per month.

Improvement in all 3 subscales of the MBI were noted at the 15-month mark, with moderate effect sizes, as calculated by standardized mean difference (SMD) of change from baseline to 15 months: emotional exhaustion SMD 0.62; 95% CI, 0.42–0.82; depersonalization SMD 0.45; 95% CI, 0.24–0.66; personal accomplishment SMD 0.44; 95% CI, 0.19–0.68. The POMS scale also showed statistically significant decreases in total mood disturbance, tension, depression, anger, and fatigue, and a statistically significant increase in vigor.[2]

A single-sample, uncontrolled pilot study in 2013 examined the effect of an abbreviated mindfulness course on measures of physician wellness and burnout.[3] Participants were 30

primary care providers (26 physicians, 3 physician assistants, and 1 nurse practitioner). Training sessions totaling 18 hours represented an abbreviated version of the mindfulness-based stress reduction course originally developed by Jon Kabat-Zinn. Participants were encouraged to practice for 10 to 20 minutes daily. Participants completed MBI at baseline and at 1 day, 8 weeks, and 9 months postintervention.

At the 9-month mark, participants showed statistically significant score improvements in all 3 subscales of the MBI compared with baseline: emotional exhaustion decreased 5.90 points (95% CI, –10.29 to –1.52; potential range 0–54), depersonalization decreased 3.51 points (95% CI, –5.91 to –1.11; potential range 0–30), and personal accomplishment increased 3.76 points (95% CI, 1.70–5.82; potential range 0-48). In this study, no effect sizes were reported.[3] EBP

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EBPEDIATRICS

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Is rivaroxaban a cost-effective anticoagulation therapy compared with warfarin?

Bottom line

Yes. For the treatment of atrial fibrillation, patients given rivaroxaban have similar or lower total costs than patients given warfarin (including medications, laboratory costs, hospitalizations, outpatient/emergency visits, and transportation) over the short term (SOR: **B**, consistent cohort studies). Rivaroxaban is also likely cost effective after 16 years compared with warfarin for treatment of nonvalvular atrial fibrillation (NVAF) (SOR: **B**, cost-effectiveness simulation). For treatment of venous thromboembolism (VTE), there is a 98% likelihood that rivaroxaban is cost saving compared with warfarin (SOR: **B**, cost-effectiveness simulation).

Evidence summary

A 2015 retrospective matched-cohort study compared the cost effectiveness of rivaroxaban versus warfarin for the treatment of NVAF.[1] Patients who were at least 18 years old and newly prescribed rivaroxaban or warfarin were matched 1:1 (2,253 in each group; N=4,506) through insurance database claims between May 2011 and December 2012. The primary outcome measured was pharmaceutical and nonpharmaceutical healthcare costs (laboratory costs, hospitalizations, emergency visits, and outpatient visits) associated with rivaroxaban and warfarin.

Pharmaceutical costs for rivaroxaban were significantly higher than warfarin (mean cost difference $2,695; 95% CI, 1,915–3,419) but no difference was found for all-cause healthcare cost of rivaroxaban (mean cost difference –$1,086; 95% CI, –$3,815 to $1,944). The mean number of days of observed therapy for rivaroxaban and warfarin were 114 and 124, respectively. The study was sponsored by the makers of rivaroxaban.[1]

A 2015 retrospective cohort compared the 30-day cost for 27 users of novel oral anticoagulants (NOACs: rivaroxaban, dabigatran, apixaban) versus 45 users of warfarin with new-onset postoperative atrial fibrillation after isolated coronary artery bypass grafting (CABG).[2]

Patients with atrial fibrillation post-CABG were recruited from a large tertiary care center. Patients with a personal history of chronic or intermittent atrial fibrillation treated with anticoagulation were excluded. Anticoagulation costs were estimated using the 30-day drug supply cost, bridging drug cost, international normalized ratio (INR) testing, transportation for INR testing, and hospitalization costs.

The mean total cost for patients in the NOAC group was significantly lower than the warfarin group ($378 vs $857; $P<.05$). The study was limited by a small sample size.[2]

A 2015 statistical analysis was designed with a 20-year horizon to predict the time to cost effectiveness for treatment of NVAF.[3] Patients were simulated to begin the study at 70 years of age with moderate risk for stroke and bleeding.

The study used the Markov model to compare NOACs (rivaroxaban, dabigatran, apixaban, edoxaban), left atrial appendage closure, and warfarin. Costs were estimated using pharmaceutical costs and INR monitoring ($91 for warfarin and $945 for NOACs per 3 months) plus adverse event costs (stroke, bleeding, etc). Cost effectiveness was established using the US willingness-to-pay threshold of $50,000 per quality-adjusted life-years (QALY) gained. The NOACs were analyzed as a single group.[3]

NOACs were found to be cost effective compared with warfarin by 16 years of use ($48,446/QALY). NOACs were associated with fewer severely disabling/fatal strokes. Study limitations included allowing for only 1 significant clinical outcome to occur per 3-month time period.[3]

A 2013 statistical analysis used the Markov model to assess the cost effectiveness of rivaroxaban versus warfarin for the prevention of recurrent VTE.[4] The model used a hypothetical cohort of 60-year-old patients given anticoagulation for 3 to 12 months after initial VTE. Costs were estimated using pharmaceutical costs and INR monitoring ($39 for warfarin and $205 for rivaroxaban per month) plus projected adverse event costs. The study transitioned simulated patients between a healthy state, major bleed, intracranial hemorrhage (ICH), and death using probabilities derived from a recent trial.

Total cost for rivaroxaban was $3,195 compared with $6,188 for warfarin. A sensitivity analysis demonstrated a 97.5% likelihood that rivaroxaban would be cost saving compared with warfarin. The authors explained that the increased cost for warfarin was because of the difference in major bleeds, ICH, and INR monitoring. Study limitations included using age 60 as the base demographic when it is unknown if bleed risk on rivaroxaban increases with age. The long-term (>12 months of therapy) risk of bleeding with rivaroxaban is not established.[4] EBP

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

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GLOSSARY

ARR=absolute risk reduction
CDC=Centers for Disease Control and Prevention
CI=confidence interval
CT=computed tomography
FDA=US Food and Drug Administration
HR=hazard ratio
LOE=level of evidence
MRI=magnetic resonance imaging
NNH=number needed to harm
NNT=number needed to treat
NSAID=nonsteroidal anti-inflammatory drug
OR=odds ratio
RCT=randomized controlled trial
RR=relative risk
SOR=strength of recommendation
SSRI=selective serotonin reuptake inhibitor
WHO=World Health Organization

EVIDENCE-BASED PRACTICE

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ISSN 1095-4120 (print)
ISSN 2473-3717 (online)

Vol 20 | No. 10 | October 2017 | Electronic Version

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

Do overweight or obese high school athletes have more athletic injuries than normal weight athletes?

EVIDENCE-BASED ANSWER

No. High school students with a body mass index (BMI) ≥85th percentile do not have an increased risk of sports-related injuries requiring medical treatment compared with normal weight students. Participation in moderate exercise 5 to 7 days per week is associated with fewer sports-related injuries in boys with a BMI ≥95% compared with lesser activity levels (SOR: **B**, cross-sectional study). The risks in younger children are unclear.

A cross-sectional study of 28,815 high school students in the United States in 2001 and 2003 assessed incidence of physical activity–related injury based on self-reported height and weight data and on student recall of a sports-related injury for which they sought medical care during the preceding 30 days.[1] Sports-related injury was not clarified with regard to type, location, severity, or other more specific definition. Students were categorized as overweight if their BMI was in the 95th percentile or higher (n=1,168) and "as at risk for overweight" if their BMI was between the 85th and 95th percentile (n=2,010). The population was adjusted for sex, race, ethnicity, grade, and type and frequency of physical activity.

Compared with normal or underweight participants, overweight or at risk for overweight high school boys or girls did not have an increased risk of sports-related injury. High-frequency participation in moderate physical activity, defined as 5 to 7 days a week of physical activity for at least 30 minutes that "did not make you sweat or breath hard" was associated with a decreased risk of a sports-related injury in overweight boys (OR 0.55; 95% CI, 0.33–0.92) compared with less physical activity.[1]

A secondary analysis of data from 2 Canadian cross-sectional surveys included 4,339 students 12 to 19 years old randomly sampled from 35 junior high schools and 24 high schools and assessed incidence of at least 1 sports injury based on 12-month recall.[2] Overweight was defined as a BMI between 20 and 24.9 (n=468); obese was defined as a BMI of at least 25 (n=247). Multivariate logistic regression analysis included adjustment for sex, age, hours of sports participation, level of play, place of residence, ethnicity, and parental education level.

Compared with healthy weight participants, injury risk was increased in obese participants (OR 1.3; 95% CI, 1.0–1.8) but not in overweight participants (OR 1.2; 95% CI, 0.93–1.6). The risk of injury requiring medical treatment was not increased in either obese or overweight participants. Subgroup analysis was not pursued for high school-aged students. Sports injury data did not include that from leisure time physical activity; furthermore, the analysis did not account for fitness level, intensity of athletic participation, type of sport, or type of injury.[2]

A Dutch cross-sectional study of 3,845 individuals 4 to 24 years old who completed a national survey assessed incidence of sports injury based on 3-month recall.[3] Sports injury was defined as "physical damage of a musculoskeletal nature" sustained suddenly during a sports activity or gradually related to sports activity. Inclusion criteria was participation in at least 1 sports activity in the past year. Overweight was defined as a BMI of at least 25 (n=567). Multiple logistic regression analysis included adjustment for activity level.

Compared with normal weight participants, overweight participants did not have an increased risk of injury (OR

0.73; 95% CI, 0.53–1.0). Given the overall low incidence of sports injuries and small subgroup size, this study did not pursue subgroup analysis for high-school-aged individuals or specific types of sports.[3]

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What is the effectiveness and safety of serial intraarticular steroid injections of the knee?

EVIDENCE-BASED ANSWER

In patients with osteoarthritis of the knee, serial intraarticular (IA) corticosteroid injections given every 3 months do not cause radiographic joint space narrowing at 2 years (SOR: **B**, single RCT). When single and serial injections are pooled, pain and function is improved in the short term (up to 6 weeks) but not the long term (after 13 weeks) (SOR: **A**, meta-analysis of RCTs). Single injections maintain symptom improvement up to 24 weeks (SOR: **A**, meta-analysis of RCTs).

In 2003, a double-blind RCT involving 68 patients with osteoarthritis of the knee compared IA triamcinolone acetonide 40 mg (50 mg prednisone equivalent) with saline given every 3 months for up to 2 years of therapy.[1] The primary outcome was radiologic progression of joint space narrowing after 2 years. Pain was also assessed on the 0–100 WOMAC (Western Ontario and McMaster Universities Arthritis Index) scale after 2 years.

Corticosteroid injections showed no deleterious effects compared with saline as measured by radiologic joint space narrowing (4.0 vs 3.9 mm; *P*=.57) at 2 years. At 2 years, IA corticosteroids showed no statistically significant difference in pain compared with saline (–11.4 vs –13.8 points; *P*=.63).[1]

A 2015 meta-analysis of 26 RCTs (N=1,749) evaluated the efficacy of single (20 RCTs) or serial (6 RCTs) IA corticosteroid injections compared with control interventions for osteoarthritic knee pain and function in adults.[2] Of the 21 studies that reported ages, the range was from 42 to 71 years old. The specific corticosteroid and dose varied among the studies, but the mean prednisolone equivalent dose was 50 mg. Study duration varied from 2 weeks to 1 year. The controls included physiologic saline (13 studies), joint lavage (4 studies), anesthetic (4 studies), viscoelastic supplementation with hyaluronic acid (4 studies), polysorbate solution (1 study), and electrostimulation for pain reduction (1 study). Subgroup analysis of just serial injections was not performed.

Overall, IA corticosteroids decreased pain more than control interventions (26 trials, n=1,749; standardized mean difference [SMD] –0.40; 95% CI, –0.58 to –0.22). The difference corresponds to a reduction of 1.0 cm on a 10-cm pain visual analog scale. Analysis based on length of follow-up revealed the effect size was significant at 1 to 2 weeks (16 trials, n=1,041; SMD –0.48; 95% CI, –0.70 to –0.27) and at 4 to 6 weeks (22 trials, n=1,529; SMD –0.41; 95% CI, –0.61 to –0.21), but was insignificant at 13 and 26 weeks. Measured on various functional scales, corticosteroid injection improved function overall (15 trials, n=1,014; SMD –0.33; 95% CI, –0.56 to –0.09), at 1 to 2 weeks (10 trials, n=763; SMD –0.43; 95% CI, –0.72 to –0.14), and at 4 to 6 weeks (12 trials, n=818; SMD –0.36; 95% CI, –0.63 to –0.09), but not at 13 or 26 weeks. No difference in safety was seen between IA corticosteroid and saline injection for adverse events, hospitalization, persistent disability, or death. The results of the included studies were heterogeneous and subject to selection and blinding bias.[2]

A 2004 meta-analysis of 10 RCTs included 6 RCTs (N=317) reporting symptom improvement outcomes after IA corticosteroid injections of the knee versus placebo injection with saline.[3] Although these 6 trials were included in the 2015 meta-analysis, the 2004 meta-analysis reported overall symptom improvement and not just pain reduction or function improvement. The 6 studies included used single injections with varying corticosteroids and doses, but the prednisone equivalent ranged from 25 to 80 mg. The various study outcome scales were dichotomized as “improved” or “not improved” with any level of improvement considered “improved.”

In pooled data analysis, single IA corticosteroid injection resulted in more patients with symptom improvement compared with placebo at 2 weeks (6 trials, n=317; RR 1.7; 95% CI, 1.4–2.0), with a number needed to treat (NNT) between 1 and 4 (3 trials, n=161). Results at 16 to 24 weeks were similar (2 trials, n=124; RR 2.1; 95% CI, 1.2–3.6), with an NNT of 4. These studies were reported as high quality. No important harms—such as transient redness, discomfort, and joint space loss—were reported.[3]

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Are antidepressants helpful for treating depression in patients with cancer?

EVIDENCE-BASED ANSWER

The answer is unclear. The evidence is conflicting concerning the effect of antidepressant medication given for depression and depressive symptoms in patients with cancer (No SOR given).

In 2015, a meta-analysis of 5 RCTs (N=226) involving cancer patients with major depression, adjustment disorder with depressed mood, or depressive symptoms evaluated the effectiveness of antidepressant medications.[1] Patients had a variety of cancers (breast, genitourinary, head and neck, thoracic, and others) at various stages. The diagnosis of depression, adjustment disorder, or depressive symptoms was made by a psychiatrist or based on responses to symptom questionnaires.

Antidepressant medications included desipramine, escitalopram, fluoxetine, mianserin (not available in the United States), and paroxetine. The primary outcome measure was a continuous measure of improvement on depression scales. Because the trials used a variety of different scales, the reviewers reported the outcome as a standardized mean difference (SMD).[1]

After 6 to 12 weeks of treatment, no difference was found in ratings of depressive symptoms for patients treated with antidepressants versus placebo (SMD –0.45; 95% CI, –1.0 to 0.11). The studies in the meta-analysis were heterogeneous in methodology and, overall, difficult to compare. Additionally, the individual RCTs analyzed were considered to be of low quality because of small sample sizes, and were at high risk of bias because of poor reporting.[1]

In 2013, a meta-analysis of 6 RCTs (N=563) evaluated effectiveness of antidepressants for the treatment of depression and depressive symptoms in patients with cancer.[2] The primary outcome of this meta-analysis was a dichotomous measure of meaningful improvement of depressive symptoms as defined by the individual studies. Only published studies were included, which excluded 1 of the unpublished studies in the meta-analysis above. This meta-analysis included 2 additional trials that had been excluded from the meta-analysis above because they provided only dichotomous outcome data on treatment response.

Patients had a variety of cancers; 3 studies (n=283) included only patients with breast cancer. Antidepressant medications included desipramine, fluoxetine, mianserin, and paroxetine, and treatment duration was 4 to 26 weeks.[2]

Antidepressants were superior to placebo in effecting a meaningful improvement in depression severity or depressive symptoms (risk ratio 1.6; 95% CI, 1.1–2.3). Limitations included the small number of trials and patients within each trial, as well as the unclear risk of bias because of lack of information concerning allocation concealment, blinding, and handling of missing data.[2]

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Are collaborative care models in the primary care environment effective for improving depression outcomes and reducing mortality in elderly patients with depression?

EVIDENCE-BASED ANSWER

The answer is unclear. Collaborative care models combining primary care providers, care managers, and mental health specialists are effective in achieving small improvements in depression symptoms, remission, and recovery rates, and quality of life among adults of all ages (SOR: **A**, meta-analysis of RCTs).

A 2012 meta-analysis of 32 RCTs examined the effect of collaborative care among primary care providers, case managers, and mental health specialists for the treatment of patients with depression (N=8,366).[1] Reviewed studies focused on adults (20–64 years) and older adults (≥65 years), and mostly white populations. Symptom improvements were measured with the Structured Clinical Interview (SCID), the Beck Depression Inventory (BDI), the Patient Health Questionnaire (PHQ9), or the Symptom Checklist (SCL-20 and SCL-90). Quality of life was measured with the Short Form Health Survey 36, EuroQoL, and the Functional Assessment of Cancer Therapy–G.

In analyses of all ages combined, collaborative care had a small effect improving depression outcomes and quality of life (QoL) (see **TABLE**) compared with usual care. A stratified analysis of adults 65 and older (6 study arms, number of patients not reported) found no significant difference in depression symptoms (standardized mean difference (SMD) 0.46; CI not reported, but $P \geq 0.5$). Substantial heterogeneity was also reported across studies.[1]

A 2014 RCT tested the long-term effects of collaborative care for depression on cardiac events and all-cause mortality among patients 60 or older during 8 years of follow-up (N=235).[2] Participants who met DSM-IV criteria for major depression, dysthymic disorder, or both were randomized into usual care (informed of diagnosis and encouraged to follow-up with their provider) or a 12-month collaborative care program involving antidepressants and psychotherapy. Study evaluators were blind to treatment assignment. Depression symptoms were assessed with the SCL-20, a 0- to 4-point scale.

No all-cause mortality differences were found (hazard ratio [HR] 0.95; 95% CI, 0.6–1.4). Intervention was associated with decrease in depression symptoms at 12 months among participants without cardiovascular disease (mean difference –0.50; 95% CI –0.70 to –0.30).[2]

A 2013 RCT included adults 60 years and older who had an upcoming physician's appointment in 1 of 20 primary care practices and examined the effect of collaborative care on all-cause mortality (N=1,226).[3] Major depression was defined by DSM-IV criteria. Minor depression was defined by DSM-IV criteria modified to require the presence of 4 depressive symptoms, Hamilton depression rating scale score of 10 or more, and a duration of at least 4 weeks. Participants were mostly female (70%), white (67%), and included patients with major (n=396) and minor depression (n=203) and no depression (n=627).

Practices randomized to usual care received educational sessions for physicians but no additional interventions for patients. Practices randomized to collaborative care included education for physicians, education for patients' families, and a depression care manager who worked with the physician to recommend treatment for patients. Median follow-up was 98 months (range 0.8–116 months).[3]

TABLE

Collaborative care for depression compared with usual care in adults[1]

Outcome	No. of RCTs[c]	Effect estimate (95% CI)
Depression symptom improvement on various depression scales	28	SMD 0.34 (0.25–0.43)
Remission (6 months)[a]	9	OR 1.7 (1.1–2.6)
Recovery (12 months)[b]	5	OR 1.8 (1.2–2.6)
Quality of life on various scales (includes functional status)	15	SMD 0.12 (0.05–0.20)

[a]Defined as a virtual absence of depression symptoms on various scales.
[b]Defined as absence of depression symptoms on various scales.
[c]Number of patients not available.
OR=odds ratio; SMD=standardized mean difference.

Compared with usual care, collaborative care for patients with major depression was associated with a 24% reduced risk of death (HR 0.76; 95% CI, 0.6–1.0). No significant effect on mortality was noted for patients with minor depression. Compared with nondepressed patients in the usual care group, patients with major depression receiving usual care had an increased risk of death (HR 1.9; 95% CI, 1.6–2.3).[3]

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How effective is physical therapy by a specialized team (with a physiatrist) in patients with cerebral palsy older than 30?

EVIDENCE-BASED ANSWER

The effect of specialized physical therapy (by a team with a physiatrist, etc) on strength and walking ability in patients with cerebral palsy (CP) over the age of 30 is unclear (No SOR given, conflicting small observational studies). Such patients may, however, have an increased perception of strength and enjoy participation in these programs (SOR: **C**, qualitative study).

A 2003 observational study recruited 17 adults (mean age 31 years) with spastic CP for a progressive strength training program to improve walking ability.[1] Individuals had to be ambulatory with or without a walking aid and not have participated in a similar program that year. The training group (n=10) used standard gymnasium equipment for 1 hour twice a week for 10 weeks and were supervised by 2 physiotherapists. The control group (n=7) did not participate in training.

Researchers measured lower extremity isometric strength, gait speed (Six Minute Walking test), and baseline spasticity by changes in tone as felt by the examiner while moving the participant's limb through its normal arc of motion (Modified Ashworth Scale).[1]

The training group showed improvement in isometric strength (hip extensors: from 11.9 to 22.4 kg; *P*=.006 and hip abductors: from 11.2 to 20.4 kg; *P*=.01), but neither change was statistically different when compared with the control group. Gait speed increased (from 0.77 to 1.01 m/s; *P*=.005) in the training group, a statistically significant difference when compared with the control group (which changed from 0.85 to 0.90 m/s; *P*=NS). Additionally, the increased gait speed in the training group compared with the control group was also significant (0.24 vs 0.05 m/s; *P*=.02). Unimpaired adults in the same mean age group have a gait speed of 1.46 m/s. Estimated spasticity did not change in either group. The study was limited by size and clinical heterogeneity.[1]

A 2004 observational study without controls recruited 10 adults (mean age 49 years) with CP for a progressive resistance strength training program led by an exercise physiologist.[2] Participants met in a gymnasium for 60 to 90 minutes twice a week for 10 weeks. Participants had to be ambulatory with or without a walking aid (n=3) or self-propel in a wheelchair (n=7) at least 10 meters and not have participated in a strength program within the previous 3 months.

The training increased leg strength from 50 to 61 kg (mean increase 11 kg; 95% CI, 2.8–19) and arm strength from 22 to 25 kg (mean increase 3.8 kg; 95% CI, 1.2–6.4). The study reported that unimpaired adults participating in a similar 10-week strength program had a 25% to 30% increase in strength. Mobility speed was not statistically different from baseline. The study was limited by using a single study group and pre-post design.[2]

A 2004 qualitative study using the same participants from the previous study examined the perceptions of patients participating in strength training programs.[3] Semi-instructed interviews using 5 open-ended questions were conducted regarding patient challenges in training, perceptions of the program, and desire to continue training as well as any personal improvements they noticed. Participants were interviewed alone or with the assistance of a caregiver (n=2) if communication barriers existed.

Most of the participants reported a positive perception of "increased strength" (n=9) and "enjoyment" (n=9) from the

program. Three perceived no physical improvement from training. This study was also limited by small size.[3]

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The opinions and assertions contained herein are those of the authors and are no to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

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Do botanicals help alleviate vasomotor symptoms?

EVIDENCE-BASED ANSWER

Black cohosh has no effect on frequency or intensity of hot flushes. Red clover may be effective, but only in the short term (3–4 months) (SOR: **A**, meta-analyses of RCTs). Genistein extracts (>30 mg daily) likely reduce the frequency of hot flushes for months to years (SOR: **A**, systematic review of RCTs).

A 2012 meta-analysis (16 RCTs, N=2,027) compared the efficacy of black cohosh at a daily median dose of 40 mg versus alternative therapies (eg, hormone replacement therapy and placebo) for treating vasomotor symptoms (VMS) in perimenopausal or postmenopausal participants.[1] VMS included hot flushes and night sweats, and the intensity and frequency of each were measured using standardized scales but intensity scales were not defined.

No significant difference was noted in the intensity (3 trials, n=214; mean difference [MD] 0.12; 95% CI, –0.06 to 0.30) or frequency (3 trials, n=393; MD 0.07; 95% CI, –0.43 to 0.56) of hot flushes per day versus placebo comparators. Nor was a significant difference noted in the frequency of night sweats in 1 trial (n=164).[1]

Another 2014 meta-analysis examined the effectiveness of red clover extract for alleviating the frequency of VMS compared with placebo in postmenopausal women (8 RCTs, N=665).[2] Six studies assessed low-dose (40–80 mg) red clover extract for 3 to 4 months, 1 study assessed high-dose (>80 mg) red clover extract for 12 months, and 1 study assessed low-dose (40–80 mg) red clover extract for 4 and 12 months.

Without considering the dose and duration of the treatment, red clover extract did not reduce hot flush frequency. However, in subgroup analysis, a significant reduction was noted in hot flushes for red clover compared with placebo at 3 to 4 months (MD –1.3; 95% CI, –1.9 to –0.77) but not at 12 months (MD 0.89; 95% CI, –0.07 to 1.9). On the other hand, neither low-dose (MD –1.7; 95% CI, –3.9 to 0.52) nor high-dose red clover (MD 1.1; 95% CI, –0.09 to 2.3) reduced hot flushes.[2]

A 2013 systematic review examined the effectiveness of products containing high levels of phytoestrogens compared with no treatment, placebo, or hormones for treating VMS in menopausal and postmenopausal women (43 RCTs, N=4,364).[3] Dietary supplements with soy extracts, red clover extract, or genistein extract (an isoflavone found in soy, fava, and other foods) containing more than 30 mg isoflavones, more than 100 µg 8-prenylnaringenin, or more than 10,000 µg total lignans were included. Efficacy was mainly determined by a change in frequency, severity, and incidence of VMS using patient diaries.

Results showed no conclusive evidence that phytoestrogens reduced the frequency or severity of VMS; however, 4 trials (n=601) that were not pooled reported doses of genistein (an isoflavone) of more than 30 mg per day significantly reduced the frequency of hot flushes by 24% to 56% compared with placebo (P<.05 in all 4 trials). These studies monitored patients for different durations, from 12 weeks to 2 years.[3]

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What is the best initial management of grade 1 or grade 2 ankle sprains?

EVIDENCE-BASED ANSWER

Nonsteroidal anti-inflammatory drugs (NSAIDs), either oral or topical, are modestly effective for decreasing pain and swelling in acute ankle sprains (SOR: **A**, meta-analysis of consistent RCTs). Supervised rehabilitation is slightly better than home exercises for reducing pain and improving ankle stability in the short term, but these differences disappear over time (SOR: **B**, systematic review of inconsistent RCTs). Current guidelines recommend NSAIDS, acetaminophen, and early mobilization as part of the initial management of ankle sprains. Evidence is insufficient regarding the value of rest, ice, compression, and elevation (RICE) (SOR: **C**, consensus and evidence-based clinical guideline).

A 2015 systematic review and meta-analysis of 22 RCTs (N=3007) compared oral or topical NSAID treatment with placebo for acute ankle sprains.[1] Trials comparing NSAIDs with other treatments and trials of chronic ankle instability and postsurgical treatment were excluded. Treatment periods varied from 4 to 14 days. Doses and types of NSAIDs varied. Primary outcomes were pain at rest or mobilization.

Oral NSAIDs were found to be slightly better than placebo for decreasing pain on a 100-mm visual analog scale (VAS) with weight bearing in the short term (<72 hours from randomization) (1 RCT, n=60; mean difference [MD] –15; 95% CI, –17 to –14) and intermediate term (72 hours to 2 weeks) (2 RCTs, n=290; MD –6.1; 95% CI, –7.4 to –4.8), pain at rest in the short term (1 RCT, n=60; MD –9.0; 95% CI, –11 to –7.2), and swelling in the short term (3 RCTs, n=173; MD –15; 95% CI, –28 to –2.4).[1]

Topical NSAIDs were found to be slightly better than placebo for decreasing pain with weight bearing in the short term (2 RCTs, n=450; MD –5.2; 95% CI, –9.9 to –0.6;) and intermediate term (2 RCTs, n=447; MD –7.0; 95% CI, –17 to –2.5;), pain at rest in the short term (4 RCTs, n=710; MD –6.5; 95% CI, –12 to –1.2), and pain at rest in the intermediate term (4 RCTs, n=706; MD –6.9; 95% CI, –11 to –3.0). Limitations included small sample sizes in some studies and study heterogeneity.[1]

A 2015 systematic review of 4 RCTs (N=286) compared clinical outcomes of supervised rehabilitation versus home exercise for the treatment of acute ankle sprains.[2] Studies were included if they were in English and analyzed patient reported outcomes or laboratory/clinical measures. Patients were 18 to 60 years old presenting to emergency departments and physician offices with acute lateral ankle sprains.

Supervised rehabilitation consisted of exercises and functional training including balance training; walking, running, and jumping exercises; supervised active range of motion; stretching; and strengthening. Patients randomized to home exercises received instruction first. The primary outcomes in 2 of the RCTs were self-reported pain, instability, and recovery at 8, 12, and 52 weeks.[2]

In 1 of these studies, patients (n=56) with more severe sprains as determined by the Ankle Function Score receiving supervised exercise demonstrated less pain at rest, less pain with walking on rough ground, less instability with walking on rough ground, and less instability with walking on flat ground 8 weeks after injury compared with the home exercise group (standardized mean differences between 0.5 and 1.5; presented in graphical form, no actual numerical data reported). No differences were noted between interventions in these same outcomes at 8 weeks in the subgroup (n=46) with less severe ankle sprains, and no differences were noted between interventions in either subgroup at longer term follow-up.[2]

Another study (n=102) showed no difference between interventions in subjective recovery at 3 months. Evidence was inconsistent for prevention of recurrent sprains, with only 1 of 3 studies showing a significant reduction in reinjury in the supervised rehabilitation group compared with the home exercise group at 12 months (number needed to treat=5; 95% CI, 5–18). Limitations included heterogeneity in outcome measures across studies and the small number of studies.[2]

The 2016 update of the Agency for Healthcare Research and Quality's national guideline on foot and ankle disorders gave recommendations on management of ankle sprains based on expert consensus from review of published RCTs, meta-analyses, and systematic reviews.[3] The guideline strongly recommended NSAIDs (strength of recommendation: A, based on ≥2 high-quality studies) and moderately recommended acetaminophen and early mobilization for acute ankle sprains (strength of recommendation: B, based on ≥1 high-quality study or multiple lower quality studies).[3]

Semirigid supports for mild and moderate sprains, rest or nonweight–bearing if unable to tolerate weight, cryotherapy, and elevation for controlling edema, which constitute RICE treatment, were not recommended based on insufficient evidence (strength of recommendation: I, evidence is insufficient or irreconcilable).[3]

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In adult patients with depression, does a diet low in refined sugars improve mood?

EVIDENCE-BASED ANSWER

The isolated effect of a low-sugar diet on mood has not been studied. When combined with other interventions, a diet low in refined sugar may improve mood in patients with depression (SOR: **B**, 2 small RCTs).

A 1990 RCT of adults (N=20) diagnosed with a major depressive episode assessed the effect of a 3-week dietary intervention low in refined sucrose and caffeine.[1] The patients were mostly (75%) female, ranging from college age to retirement age, who had their first major depressive episode at a mean age of 22 years (median number of episodes, 10).

Inclusion criteria included a Beck Depression Inventory (BDI) of more than 15, a Minnesota Multiphasic Personality Inventory-Depression (MMPI-D) of more than 69, a Christensen Dietary Distress Inventory of more than 12, and a current episode of major depression using DSM-III-R criteria. Exclusion criteria included bipolar depression, psychotic symptoms, active substance abuse, organic brain disorders, concurrent treatment, and current active suicidal ideation.[1]

The intervention group was instructed to eliminate refined sucrose and caffeine from their diet and given a list of recommended foods. Adherence was measured using a saliva assay for caffeine and a food record sheet. The recommended control diet was low in red meat and artificial sweetener. Three scales of symptom severity (see **TABLE 1**) were used to assess outcomes at the end of the 3-week intervention period.[1]

TABLE 1

Depression scales and inventories used in 1990 RCT of caffeine and refined sucrose[1]

Scale name	Description
Minnesota Multiphasic Personality Inventory-Depression	57-item depression scale, raw scores are transformed into T-scores with a mean of 50 and standard deviation of 10
Beck Depression Inventory	21-item depression scale, with item scores of 0–3 and total possible score of 63
Symptom Checklist 90	90-item scale, with item scores of 0–4, and total possible score of 360 transformed into T-scores

The intervention diet reduced depression scores from baseline more than the control diet on the MMPI-D (mean difference [MD] 27 vs 4.6; $P<.05$), BDI (MD 18 vs 4.3; $P<.05$), and Symptom Checklist 90 (MD 19 vs 6.2; $P<.05$).[1]

A 2012 RCT of adults (N=80) diagnosed with depressive disorders in Spain evaluated the effectiveness of 4 lifestyle recommendations as an add-on treatment to antidepressant medications for 6 months.[2] The mean age was about 50 years. No differences were noted in the mean number of previous episodes of depression (2.5 vs 2.6) or in duration of the current episode (33 vs 40 months). Both groups included patients taking various pharmacotherapies, including SSRIs (24 vs 16), SNRIs (12 vs 16), tricyclics (7 vs 14), and "other antidepressants" (6 vs 8).

The intervention group received written instructions to "try to eat a healthy and balanced diet. Eat at regular hours without snacking between meals. Avoid especially sweet or sugary drinks. Eat fish at least 3 times per week, plus fruit, cereals, nuts, and vegetables daily." The intervention group nondietary instructions were to sleep approximately 10 hours daily and not nap during the day, to walk at least 1 hour per day then shower or bathe afterward, and to get at least 2 hours of sun exposure daily while avoiding sunburn. The control group received more general written advice to "try

TABLE 2

Changes in depression scales and inventories with multicomponent lifestyle intervention[2]

Name	Description	Timing	Intervention scores	Control scores	*P*
Hamilton Depression Scale	17-item scale with item scores of 0–2 or 0–4; total score interpreted as follows: 0–7: normal 8–13: mild depression 14–19: moderate depression 19–22: severe depression ≥23: very severely depressed	Baseline	20	20	.67[a]
		6 months	11	17	<.01
Beck Depression Inventory-II	21-item depression scale, with item scores of 0–3; total score interpreted as follows: 0–13: minimal depression 14–19 mild depression 20–28: moderate depression 29–63: severe depression	Baseline	25	27	.35[a]
		6 months	16	22	.03
Global Clinical Impression Scale	7-point clinician assessed scale 1: normal, not at all ill 2: borderline mentally ill 3: mildly ill 4: moderately ill 5: markedly ill 6: severely ill 7: extremely ill	Baseline	4.0	4.2	.31[a]
		6 months	2.4	3.5	<.01

[a]Not statistically significant.

to eat a healthy and balanced diet," "sleep the hours... your body needs," "adapt... daily physical activity to meet your needs best," and to "take precautions to avoid sunburn..." Three different scales were used to assess outcomes (see **TABLE 2**).[2]

No differences were noted between groups in baseline scores and scores decreased in both groups over the course of the trial; however, the scores in the intervention group were significantly lower than the control group at the end of the trial (see **TABLE 2**). The study was limited by the inclusion of patients with dysthymic and bipolar disorder.[2]

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When should we obtain images for an older adult with acute vertigo?

EVIDENCE-BASED ANSWER

For older adults with acute vertigo for more than 24 hours, normal HINTS or HINTS Plus examinations have negative likelihood ratios of 0.04 or less, making them good for ruling out stroke and likely precluding the need for imaging. Patients with positive HINTS or HINTS Plus examinations should undergo imaging. The ABCD2 score has a lower sensitivity and should not be used for ruling out stroke (SOR: **A**, systematic review of observational studies and 2 additional cross-sectional studies).

A 2011 systematic review of 10 cross-sectional, case series, and case-control studies (N=392) examined bedside predictors of stroke in adults with acute vestibular syndrome (AVS) defined as acute, prolonged (>24 hours) vertigo.[1] Included studies used a reference standard of

TABLE

Diagnostic test properties of bedside stroke predictors compared with brain MRI in patients with acute, prolonged vertigo[1,2]

Test	No. of studies	No. of patients	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
HINTS[1]	2	184	98	85	6.2	0.02 (0.01–0.09)
HINTS[2]	1	190	97 (92–99)	84 (75–91)	6.2 (3.7–10)	0.04 (0.02–0.11)
HINTS Plus[2]	1	190	99 (96–100)	83 (74–90)	5.9 (3.6–9.6)	0.01 (0.00–0.08)
ABCD2 ≥4[2]	1	190	61 (52–70)	62 (51–73)	1.6 (1.2–2.2)	0.62 (0.47–0.83)
Test of Skew[1]	2	184	30 (22–39)	98 (95–100)	20 (2.8–140)	0.71 (0.63–0.80)
Head Impulse Test[1]	4	216	85 (79–91)	95 (90–100)	18 (6.1–55)	0.16 (0.11–0.23)
Head Impulse Test[2]	1	190	90 (84–95)	87 (78–93)	7.0 (3.9–12)	0.11 (0.06–0.20)
Direction-changing Nystagmus[1]	6	320	38 (32–44)	92 (86–98)	4.5 (2.2–9.3)	0.68 (0.60–0.76)

ABCD2=age, blood pressure, clinical features, duration of symptoms, diabetes; HINTS=head impulse test, nystagmus, test of skew; HINTS plus=HINTS plus new hearing loss detected by finger rubbing; LR+=positive likelihood ratio; LR– =negative likelihood ratio; MRI=magnetic resonance imaging.

brain computed tomography (CT) or magnetic resonance imaging (MRI) to diagnose stroke.

The strongest predictive factor was a HINTS examination, which includes 3 bedside physical examination tests: head impulse test (the patient maintains forward fixation while the examiner moves the patient's head 10 degrees to the right and left with absence of saccade concerning for a stroke), direction-changing nystagmus, and test of skew (vertical misalignment of eyes revealed by cover/uncover test). If any single test result is abnormal, the HINTS examination is considered positive.[1]

The HINTS exam was moderately effective for ruling in stroke and very effective for ruling out stroke (see **TABLE**). The individual components of the HINTS examination were not as effective for ruling out stroke. The review did not state who performed the bedside examinations.[1]

A 2013 prospective cohort study of 190 adults presenting to the emergency department with AVS and at least 1 stroke risk factor (including prior stroke, hypertension, or diabetes) compared HINTS and ABCD2 risk score for diagnosing stroke.[2]

The ABCD2 score is compiled with age (≥60 years=1 point); blood pressure (≥140/90 mmHg=1 point); clinical features (unilateral weakness=2 points, speech disturbance without weakness=1 point); duration of symptoms (10–59 minutes=1 point and ≥60 minutes=2 points); and diabetes (1 point), with 4 or more points considered a positive result.

Patients (median age 61 years, 90% white, 61% male) had nystagmus and continuous vertigo. A neuro-ophthalmologist performed the HINTS and neurologic examinations followed by neuroimaging within 24 hours (97% by MRI). If the MRI result was negative and stroke was strongly suspected, an MRI was repeated in 48 hours. Nonstroke patients were followed for 3 months and none were diagnosed with stroke. A normal HINTS and HINTS combined with new hearing loss were better at ruling out stroke than the ABCD2 (see **TABLE**). An abnormal HINTS examination had a positive likelihood ratio of 64 for any central cause of vertigo (including stroke, brain mass, multiple sclerosis). The overall stroke prevalence was 60%.[2]

A 2015 cross-sectional study assessed bedside predictors of stroke in adults (N=272, median age 56 years) with acute, continuous dizziness.[3] Patients had either nystagmus or new gait imbalance. The reference standard was brain MRI, and neurology-trained examiners were blinded to the MRI results. Stroke prevalence was 11%.

An ABCD2 score of more than 4 increased the odds of stroke (odds ratio [OR] 1.7; 95% CI, 1.2–2.5) as did "other CNS features" such as visual field disturbance, sensory

problems, or dysmetria (OR 2.5; 95% CI, 1.1–6.1). A positive HINTS did not significantly increase the odds of stroke (OR 2.8; 95% CI, 0.96–8.3). The inclusion of patients without nystagmus may have decreased the reliability of the HINTS examination, and interrater reliability for the ocular motor examination was fair.[3]

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What are the most effective treatments for decreasing pain of plantar fasciitis?

EVIDENCE-BASED ANSWER

The answer is unclear, but calcaneal antipronation taping and prefabricated heel cups/pads are better than stretching, and prefabricated heel cups/pads are better than full-length custom orthoses. The combination of night splints and full-length orthoses is better than orthoses alone (SOR: **B**, RCTs). Moderate-intensity extracorporeal shockwave therapy (ESWT) and botulinum toxin type A injections are effective but comparison with other interventions is unknown (SOR: **B**, subgroup meta-analysis of RCTs and single RCT). Night splints, prefabricated or custom-made orthoses, and taping are recommended treatments (SOR: **C**, expert opinion).

A 2008 systematic review included 2 RCTs (N=133) that examined the effect of taping on pain in patients with plantar fasciitis.[1]

The first trial (n=92) looked at the effect of 1-week application of antipronation taping plus one 3-minute session of sham ultrasound versus sham ultrasound alone on "first-step" pain (defined as the pain when first standing from bed in the morning) measured by a 100-point visual analog scale (VAS). At 1 week, antipronation taping plus sham ultrasound improved "first-step" pain from baseline 12 points more than sham ultrasound alone (95% CI, 2.2–22).[1]

The second RCT (n=41) compared the effect of calcaneal taping with sham taping and with plantar fascia stretches on absolute pain scores measured on a 10-point VAS. At 1 week, the mean pain score for calcaneal taping (2.7 points) was significantly better than for sham taping (6.0 points) and stretching (4.6 points; $P<.001$ for both comparisons).[1]

A 1999 RCT (N=236) evaluated stretching alone compared with stretching plus 4 different shoe inserts (prefabricated silicone, rubber, or felt heel cups/pads; and custom orthosis) for plantar heel pain.[2] The outcome was pain evaluated by a patient questionnaire that was dichotomized into improved pain (responders) or stable/worse pain (nonresponders).

When analyzed as a group at 8 weeks, the prefabricated orthoses plus stretching had a higher response rate than stretching only and custom orthoses plus stretching (88% vs 72%, $P=.022$; and 88% vs 68%, $P=.0074$, respectively).[2]

A 2012 RCT (N=28) of adult patients with plantar fasciitis compared full-length foot orthoses and night splints versus foot orthoses alone on pain over 8 weeks.[3] Using a questionnaire, patients rated 9 aspects of pain, each on 10-cm VAS, with a maximum pain score of 90.

At 8 weeks, night splints and orthoses decreased pain from baseline 21 points more than orthoses alone ($P=.01$).[3]

A 2013 meta-analysis of 11 RCTs (N=1,287) evaluated ESWT compared with placebo intervention for treating adults with chronic plantar fasciitis pain unresponsive to conservative measures.[4] ESWT intervention included 1 to 3 sessions spaced 1 to 4 weeks apart of low-, moderate-, or high-intensity ESWT. Overall pain reduction was measured on a 0- to 10-VAS.

Pooling all ESWT intensities revealed no difference in overall pain; however, the subgroup of moderate ESWT versus placebo showed a significant improvement in overall pain (3 trials, n=369; weighted mean difference 6.6; 95% CI, 6.4–6.7). Low-intensity and high-intensity ESWT had no effect on overall pain.[4]

A 2010 RCT (N=50) compared ultrasound-guided injections of botulinum toxin type A versus saline for treating plantar fasciitis pain.[5] Pain was measured on a 10-point VAS scale at 3 weeks and 3 months after injections.

The botulinum toxin type A group had lower mean VAS

pain scores than the saline group at 3 weeks (3.4 vs 5.1; *P*<.001) and 3 months (2.0 vs 5.2; *P*<.001).[5]

A 2014 Clinical Practice guideline from the American Physical Therapy Association on treatment of plantar fasciitis recommends night splints, prefabricated or custom-made orthoses, and taping (grade of recommendation A, based on well-done RCTs and prospective cohort studies).[6]

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Is care in conjunction with consultation liaison psychiatry better than standard care for adults with mental health disorders seen in a primary care setting?

EVIDENCE-BASED ANSWER

Treating mental health disorders in a primary care setting using a consultation liaison model improves mental health outcomes versus standard care, but improvement is limited to 3 months after beginning treatment, and applies mainly to patients with depression without suicidal ideation (SOR: **B**, meta-analysis of low-quality RCTs). No outcome differences were noted 12 months or longer after treatment initiation (SOR: **B**, meta-analyses of low-quality RCTs).

A 2015 systematic review and meta-analysis of 12 RCTs (N=2,605) compared the effectiveness of consultation liaison psychiatry versus standard care for adults (>18 years old) with mental health disorders in a primary care setting.[1] The trials were conducted in North America or Europe and included a mix of newly diagnosed and previously diagnosed mental health conditions. Eight trials included patients with depression alone, and 1 trial each evaluated patients with anxiety or somatoform disorder, medically unexplained symptoms, problem drinking, or various mental disorders. The trials excluded patients with suicidality, schizophrenia, bipolar disorder, dementia, posttraumatic stress disorder, and significant alcohol or substance abuse.

Consultation liaison psychiatry was defined as at least 1 contact between the primary care provider (PCP) and a mental health specialist; however, the frequency and method of contact were both variable. Contact between a mental health specialist and the patient was also common, but 2 studies involved only contact between the PCP and the mental health specialist. Standard care involved PCP treatment with referral to psychiatry at the PCP's discretion. Improvement in mental health was defined as a 50% reduction in Symptom Checklist (SCL)-90 or asymptomatic on the 9-symptom Structured Clinical Interview for DSM-IV.[1]

Consultation liaison psychiatry improved mental health for up to 3 months after the start of treatment, but no differences were noted in mental health or depression symptoms scores at 3 to 12 months (see **TABLE**). Consultation liaison psychiatry also improved multiple secondary outcomes. The trials were generally low quality because of inadequate blinding or incomplete outcomes reporting.[1]

A 2010 systematic review and meta-analysis of 3 RCTs and 2 cluster randomized trials (N=1,065), none of which were blinded and 3 of which were included in the 2015 systematic review cited above, studied the role of consult liaison psychiatry for the management of depression in primary care over longer periods.[2] The trials included adult primary care patients with a diagnosis or symptoms of depression. Consultation liaison was defined as an intervention in which patients were seen once or twice by a mental health professional for assessment and advice to the primary provider about management,

TABLE

Consultation liaison versus standard care for people with mental health disorders in primary care[1]

	Time period (months)	No. of trials	N	% Risk difference[a] (95% CI)	NNT
Primary outcome					
Improvement in mental disorder	0–3	2	445	13 (4–22)	8
	3–12	2	678	6 (–5 to 18)	N/A
Secondary outcomes					
Consumer satisfaction	0–3	1	228	31 (21–40)	3
	3–12	2	445	12 (6–19)	8
Consumer adherence	3–12	7	1,251	16 (8–24)	6
Adequate treatment by primary care provider	3–12	3	797	15 (6–24)	7
Prescribing pharmacological treatment	3–12	4	796	8 (2–15)	13

[a]A positive result favors consultation liaison.
N/A=not applicable; NNT=number needed to treat.

but in which no treatment was provided by the mental health professional.

The consultation liaison model of care did not alter short term (<12 months) depression outcomes (3 trials, n=721; standardized mean difference [SMD] −0.04; 95% CI, −0.21 to 0.14), long term (>12 months) depression outcomes (3 trials, n=560; SMD 0.06; 95% CI, −0.13 to 0.26), or use of antidepressants (3 trials, n=718; risk ratio 1.2; 95% CI, 0.91–1.7). All of the trials were at high or unclear risk of bias in at least 3 of the 6 quality domains.[2] EBP

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A depressing view of hormonal contraception?

Skovlund CW, Mørch LS, Kessing LV, Lidegaard Ø. Association of hormonal contraception with depression. *JAMA Psychiatry*. 2016; 73(11):1154–1162.

A 2016 prospective cohort study (with 1,061,997 women 15–34 years old in the Danish Sex Hormone Register Study) evaluated the association between hormonal contraceptive use and subsequent antidepressant use or diagnosis of depression from 2000 to 2015. Exclusion criteria included a prior diagnosis of depression or use of an antidepressant. The 2 primary outcomes were initial use of an antidepressant or an initial outpatient or inpatient diagnosis of depression.

Women prescribed oral combined hormonal contraception were found to be at increased risk for a diagnosis of depression (rate ratio [RR] 1.2; 95% CI, 1.22–1.25) and antidepressant prescriptions (RR 1.1; 95% CI, 1.08–1.14). Women prescribed progestin-only hormonal contraception also had an increased risk of both endpoints (RR 1.3; 95% CI, 1.27–1.40 and RR 1.2; 95% CI, 1.04–1.31, respectively). The peak timing of both outcomes was 6 to 12 months after initiating contraception.

In subgroup analysis, adolescents prescribed oral combined hormonal contraception were also at greater risk for a diagnosis of depression (RR 1.8; 95% CI, 1.75–1.84) and for receiving antidepressant prescriptions (RR 1.7; 95% CI, 1.63–1.81). Adolescents prescribed progestin-only contraceptives were at increased risk in both endpoints (RR 2.2; 95% CI, 1.99–2.52 and RR 1.9; 95% CI, 1.49–2.53, respectively).

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

Bottom line: This study demonstrated an association between the initiation of hormonal birth control and a new depression diagnosis or antidepressant use. The endpoints used had drawbacks (ie, antidepressants are often prescribed for diagnoses other than depression) and it is unclear if these findings would change practice beyond medication counseling.

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

Rewrite the blackbox warning? Risperidone use in elderly patients with dementia

Howard R, Costafreda SG, Karcher K, Coppola D, Berlin JA, Hough D. Baseline characteristics and treatment-emergent risk factors associated with cerebrovascular event and death with risperidone in dementia patients. *Br J Psychiatry*. 2016; 209(5):378–384.

This meta-analysis of 6 RCTs that included 1,712 patients evaluated variables associated with cerebrovascular adverse events (CVAE) or mortality in elderly patients with dementia.

All trials were conducted by the pharmaceutical company Janssen; 2 trials were stopped early for business reasons and not published, while the other 4 were published.

Patients in each trial were at least 55 years old, had a diagnosis of dementia, and received either risperidone or placebo. Outcomes included identifying baseline characteristics and treatment-emergent factors associated with increased or decreased risk of CVAE or mortality.

No difference was noted in CVAE in patients depressed mood treated with risperidone versus patients with depressed mood treated with placebo (3.6% [4 of 112] vs 6% [3 of 54]; hazard ratio [HR] 0.54; 95% CI, 0.12–2.4). The rate of CVAE was higher for patients treated with risperidone versus placebo who did not have depressed mood (5.1% [45 of 877] vs 1.3% [8 of 639]; HR 4.2; 95% CI, 2.0–8.8). Mortality was unchanged in patients with depressed mood treated with risperidone compared to placebo.

The use of anti-inflammatory medications increased mortality in the risperidone group compared with placebo (5.2% [16 of 310] vs 1.4% [3 of 213]; HR 3.4; 95% CI, 1.0–12). Rates of mortality were similar for both groups in patients who did not take anti-inflammatory medications.

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

Bottom line: Avoiding risperidone may not be necessary for all elderly patients with dementia. CVAE rates were no different from those of placebo for patients with depressed mood who received risperidone. Clinicians should continue to weigh risks and benefits for using antipsychotic agents in elderly patients with dementia. EBP

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