

EVIDENCE-BASED PRACTICE

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Vaccinophilia/phobia

I like vaccines. In my esteem, they rank right up there with other great public health measures like potable water testing and sewage treatment. Okay, those are not glamorous comparisons, but few things are better for controlling pestilence than clean water, closed sewers, and vaccines.

I like vaccines because they have allowed me to visit bat caves in Thailand and not worry quite so much about rabies. They let me go to the Peruvian Amazon and not worry about yellow fever. They let me hang out in my own back yard and not worry about meningitis from the kids next door or tetanus from the rusty nails in the woodpile. If there is a vaccine for it, I want that vaccine. Today!

So I find it most perplexing that some people do not like vaccines and prefer their children not get them. I have several such families in my office practice. But until recently, I saw no reason to get worked up about a few isolated vaccine deniers scattered about the rural areas of the county. Of course, it would be another matter if these families clustered together: such behavior would effectively create a biological time bomb.

Unfortunately, that is exactly what vaccine deniers do—they cluster! This was vividly demonstrated in a study that reviewed all the school vaccine exemption forms collected by the California Department of Public Health.¹ In the urban cores and the central valley of California, vaccine refusals were rare. But in the suburban schools, vaccine refusal rates were as high as 79%. Refusal rates were highest in schools that were private, white, and located along the coast. The results were clear: upper middle-class suburban whites had created large, dense, at-risk populations of innocent kids.

I'm thinking maybe these rich schools need to spend a little more time on topics like the Black Death and Spanish Flu in history class. Then maybe throw in some Edward Jenner and Jonas Salk. It's captivating reading and it takes only one major plague to see the wisdom of vaccination.

That wisdom has been taught before. I don't want to learn it again.



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

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Do thiazide diuretics cause insulin resistance?

EVIDENCE-BASED ANSWER

Treatment of hypertension with thiazide-type diuretics is associated with a higher risk of hyperglycemia and of developing type 2 diabetes (DM2) than treatment with other classes of antihypertensive medications (SOR: **A**, meta-analysis of RCTs and subsequent RCTs).

Evidence summary

A 2007 network meta-analysis of 22 RCTs (N=143,153) evaluated the new diagnosis of DM2 in patients treated with oral antihypertensive agents at standard doses.¹ The network meta-analysis allowed the comparison of trials with different treatment strategies and provided point estimates of associations with given endpoints, even when treatments were only indirectly compared. The main outcome of this meta-analysis was the proportion of patients who developed DM2.

Compared with placebo, treatment with thiazide diuretics was associated with an increased risk of DM2 (odds ratio [OR] 1.3; 95% CI, 1.1–1.6). When compared with thiazide treatment as the referent standard, all other medication classes were associated with a lower incidence of DM2 except beta-blockers. ARBs had the lowest odds of developing DM2 versus diuretics (OR 0.57; 95% CI, 0.46–0.72), followed by ACE inhibitors (OR 0.67; 95% CI, 0.56–0.80), calcium channel blockers (OR 0.75; 95% CI, 0.62–0.90), and placebo (OR 0.77; 95% CI, 0.63–0.94). Compared with diuretics, beta-blocker treatment did not show a significantly lower risk of DM2 (OR 0.9; 95% CI, 0.75–1.1).¹

Limitations of the study included the rarity of incident DM2 as a study endpoint and changes to diagnostic criteria for DM2 over time. Although the study demonstrated an association between antihypertensive agents and DM2, it did not prove a causative relationship.¹

A 2010 RCT (N=9,306) evaluated cardiovascular outcomes and conversion to DM2 in patients with impaired glucose tolerance who were treated with antihypertensive and diabetes medications. In 2013, the data were reanalyzed to evaluate the effect of diuretics on the development of DM2 in patients with impaired glucose tolerance.² Out of 6,346 diuretic-naïve patients, 1,316 (21%) started diuretic therapy. The median duration of follow-up for DM2 was

5 years. DM2 was diagnosed by measuring plasma glucose levels every 6 months for 3 years and then yearly thereafter.

Patients started on diuretics were significantly more likely to develop DM2 than were patients who were not started on diuretic therapy (hazard ratio [HR] 1.2; 95% CI, 1.1–1.4; number needed to harm [NNH] 17; 95% CI, 9–68).²

A large 2002 RCT (N=42,418) that compared different classes of antihypertensive drugs and their effects on mortality and cardiovascular events was reevaluated through a post hoc subgroup analysis in 2006. This post hoc analysis compared the effects of antihypertensive agents on fasting glucose levels.³ The study included patients ≥ 55 years old with blood pressures ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic. Patients with ≥ 1 coronary heart disease risk factor and those taking antihypertensives with a blood pressure $< 160/100$ mmHg were also included. Patients without DM2 (N=18,411) were randomized to receive chlorthalidone, amlodipine, or lisinopril. Fasting glucose levels were measured and noted to rise in all groups.

After 2 years of treatment, fasting glucose levels increased 8.5 mg/dL with chlorthalidone, 5.5 mg/dL with amlodipine, and 3.5 mg/dL with lisinopril. The odds of developing DM2 were significantly lower with lisinopril versus chlorthalidone (OR 0.55; 95% CI, 0.43–0.70) and amlodipine versus chlorthalidone (OR 0.73; 95% CI, 0.58–0.91). The lisinopril and amlodipine groups continued to have lower odds of developing DM2 than the chlorthalidone group at 4 and 6 years.³

Limitations included inconsistent measurements of blood glucose, with only 53% of the 18,411 patients in this study having had 1 or more fasting glucose levels recorded during follow-up. Also, the initial study was not designed to look specifically at the development of DM2.³

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BMI: A weighty risk for complex endometrial hyperplasia

Wise MR, Gill P, Lensen S, et al. Body mass index trumps age in decision for endometrial biopsy: cohort study of symptomatic premenopausal women. *Am J Obstet Gynecol.* 2016; 215(5):598.e1–598.e8.

This retrospective cohort study was carried out to determine whether a body mass index (BMI) of 30 kg/m² or more affected the likelihood of finding complex endometrial hyperplasia, complex atypical hyperplasia, or endometrial cancer on endometrial biopsy in women 55 years old or younger with abnormal uterine bleeding.

The study included 916 premenopausal women residing in Auckland, New Zealand with a diagnosis of abnormal uterine bleeding referred for endometrial biopsy between 2008 and 2014, and excluded women with a history of endometrial cancer. The primary outcome was histologic diagnosis of endometrial hyperplasia with or without atypia or endometrial cancer.

Using multivariate logistic regression, patients with a BMI of 30 kg/m² or more were more likely to have the primary outcome than patients with a BMI of less than 25 kg/m² (adjusted odds ratio 4.0; 95% CI, 1.4–12). In the study population, about half of the participants had a BMI of 30 kg/m² or more and 4.9% of women overall were diagnosed with complex hyperplasia with or without atypia or cancer.

Women of Indian or Pacific Islander descent had higher odds of the primary outcome and were also more likely to be obese, such that multivariate analysis was not able to distinguish between both characteristics. Other significant risk factors were anemia, nulliparity, and thickened endometrium on ultrasound. Age, diabetes, and menstrual history were not risk factors. Results may not be generalizable to populations with lower level of obesity and different ethnic composition.

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

Bottom line: For patients with premenopausal abnormal uterine bleeding, consider using BMI as an indication for endometrial biopsy, regardless of age.

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Bursting the bubble: Chewing gum for prevention of postoperative ileus

Short V, Herbert G, Perry R, et al. Chewing gum for postoperative recovery of gastrointestinal function. *Cochrane Database Syst Rev.* 2015; (2):CD006506.

This meta-analysis of 81 RCTs (N=9,072) compared chewing gum with placebo after abdominal surgery to determine if gum chewing hastens the return of gastrointestinal function. Subgroup analyses were performed for colorectal surgery, cesarean section, and other surgery. The analysis included all RCTs that assessed chewing gum as monotherapy versus control in the immediate postoperative period.

Primary outcomes included time to first flatus and time to first bowel movement. Secondary outcomes included length of hospital stay, time to first bowel sounds, and adverse events. Study quality was affected by lack of blinding and lack of standardized protocols.

Gum chewing was associated with an overall reduction in time to first flatus of 10.4 hours (95% CI, –11.9 to –8.9), with decreases of 12.5 (95% CI, –17.2 to –7.8), 7.9 (95% CI, –10.0 to –5.8), and 10.6 (95% CI, –12.7 to –8.5) hours in colorectal surgery, cesarean section, and the other surgery subgroups, respectively.

There was an overall decrease in time to first bowel movement of 12.7 hours (95% CI, –14.5 to –10.9). In that subgroup analysis, chewing gum was associated with a reduction of 18.1 hours (95% CI, –25.3 to –10.9) for colorectal surgery, a reduction of 9.1 hours (95% CI, –11.4 to –6.7) for cesarean section, and a reduction of 12.3 hours (95% CI, –14.9 to –9.7) for other surgery.

Significant decreases in length of hospital stay (0.7 days; 95% CI, –0.8 to –0.5) and time to first bowel sounds (–5.0 hours; 95% CI, –6.4 to –3.7) were found. Similar prevalence of adverse events were found across studies.

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

Bottom line: Chewing gum after abdominal surgery decreases risk of ileus across many RCTs, with few adverse events. However, overall study quality was low. EBP

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How long do you need to treat bacteremia in a stable patient?

CASE

A 57-year-old man with a history of type 2 diabetes mellitus, hypertension, and chronic lower extremity edema was admitted to the hospital with redness, swelling, and pain around a right lower extremity ulcer. He was initially found to have a fever and tachycardia, which resolved with IV fluids and acetaminophen. Blood cultures revealed *Staphylococcus aureus* and the patient was started on appropriate antibiotic therapy. How long should antibiotic therapy be administered to this patient?

Review of evidence

A 2011 systematic review and meta-analysis of 24 RCTs explored rates of clinical cure, microbiologic cure, and survival among 155 patients randomly assigned to short- (5–7 days) or long-term (7–21 days) treatment with the same antibiotic regimen.¹ One trial was dedicated to bacteremia in neonates, while the remainder looked at bacteremic adult patients with intra-abdominal infections, pyelonephritis, skin and soft tissue infection, and pneumonia.

No differences were noted in rates of clinical cure (not defined) (7 trials, n=101; risk ratio [RR] 0.88; 95% CI, 0.77–1.01), microbiologic cure (7 trials, n=60; RR 1.1; 95% CI, 0.91–1.2), or survival (7 trials, n=46; RR 0.97; 95% CI, 0.76–1.2).¹

A 2013 prospective observational cohort study examined outcomes between varied antibiotic treatment durations in 111 patients with uncomplicated *S aureus* bacteremia without endocarditis.² Patients were assigned to treatment durations of <14 days or >14 days and followed for 12 weeks for treatment failure (defined as relapse of bacteremia), deep-seated infection (not defined further), or death. While treatment failure did occur less commonly in the longer treatment group, the difference was not statistically significant (7.9% vs 1.4%; $P=.64$).

A meta-analysis of 7 RCTs in European intensive care units (ICUs) from 2003 to 2009 considered the use of procalcitonin levels in guiding the duration of antibiotic therapy in adult patients with sepsis.³ The trials followed ICU patients throughout their hospital stay and, when combined for analysis as a secondary outcome, showed a significantly shorter median duration of antimicrobial therapy when either a low procalcitonin level or specific percent decline in procalcitonin level was used as a marker for termination of treatment (hazard ratio [HR] 1.3; 95% CI, 1.01–1.5). These results

were significant in conjunction with the primary outcomes of no differences in hospital or 28-day mortality rates among patients with severe sepsis (the diagnosis of bacteremia among septic patients was not reported).

CASE WRAP-UP

Shorter duration antibiotic therapy (5–7 days) appears adequate for treatment of bacteremia in a hemodynamically stable patient. Procalcitonin levels may be used to help decide duration of therapy in patients with sepsis. For our patient, the inpatient team decided he was hemodynamically stable and clinically improving after 7 days of antibiotics and elected to discontinue antibiotics at that time. The patient was discharged home with no complications.

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When should we stop mammography screening for breast cancer in elderly women?

EVIDENCE-BASED ANSWER

The answer is unclear. Mammography screening provides no mortality benefit for women aged 70 to 74 years (SOR: **A**, systematic reviews of 2 RCTs). However, mammography screening is recommended every 2 years by the US Preventive Services Task Force (USPSTF) and every 2 to 3 years by the Canadian Task Force on Preventive Health Care (CTFPHC) for women aged 70 to 74. Neither guideline provides a recommendation for women older than 74 years (SOR: **C**, consensus guidelines).

A 2009 systematic review conducted for the USPSTF evaluated whether screening mammography decreased breast cancer mortality in average-risk women aged 40 to 49 years and 70 to 74 years.¹ Only 1 RCT was included that evaluated older women aged 70 to 74. This RCT reported 17-year follow-up (range 15.8–18.6 years) data on women aged 40 to 74 from Östergötland county, Sweden (N=92,782 total and n=9,932 for 70–74 age group).² Women were randomized to screening mammography or control using cluster randomization with geographic area and then via supervised coin toss. Women aged 70 to 74 years underwent 2 screening rounds 33 months apart. Exclusion criteria included a diagnosis of invasive epithelial breast cancer before randomization and no permanent address.

Mammography led to no statistically significant reduction in breast cancer mortality in the 70 to 74 age range compared with control (relative risk [RR] 1.1; 95% CI, 0.73–1.7). Despite this finding, the USPSTF recommended biennial screening mammography for average-risk women aged 50 to 74 based on this systematic review (Grade B, “high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial”). The USPSTF provided no recommendation for women 75 years and older due to insufficient evidence on risks and benefits (Grade I, “current evidence is insufficient to assess the balance of benefits and harms”).²

A 2011 systematic review for the CTFPHC also evaluated mammography in average-risk women defined as no personal or first-degree relative history of breast cancer, no BRCA gene mutations, and no chest wall radiation exposure.³ For the 70–74 age group, this review included the same RCT as the review above, but added an older RCT. It is unclear why both studies were not included in the 2009 review. The older RCT reported 13-year follow-up data in women aged 40 to 74 from both Kopparberg and Östergötland counties, Sweden (N=133,065 total and n=17,646 for 70–74 age group).⁴ Women were randomized to screening mammography or control using cluster randomization with geographic area. Mammography screening was obtained every 24 months for women aged 40 to 49 and every 33 months for women aged 50 and older.

Overall, mammography screening led to no statistically significant reduction in breast cancer mortality in the 70–74 age range (RR 0.79; 95% CI, 0.51–1.2). Pooled analyses of the 17-year follow-up data of women from Östergötland county and 13-year follow-up data of women from Kopparberg county (the longest follow-up available in each group) also found that in women aged 70 to 74 years (n=17,646) there was no statistically significant decrease in breast cancer mortality in the mammography group (RR 0.68; 95% CI, 0.45–1.01). However, the CTFPHC recommended screening every 2 to 3 years in women aged 70 to 74 years (weak recommendation; low-quality evidence) due to the magnitude of cancer mortality reduction with screening being similar to the reduction from screening in women aged 50 to 69 (n=250,274; RR 0.79; 95% CI, 0.68–0.90). There was no data addressing the benefits of screening mammography in women older than 74 years.

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Does rotavirus vaccination reduce deaths from diarrheal illness in infants?

EVIDENCE-BASED ANSWER

Rotavirus immunization does not appear to decrease mortality (SOR: **B**, single RCT), however, it does decrease any rotavirus gastroenteritis (RG), severe gastroenteritis, and very severe gastroenteritis (SOR: **A**, RCTs).

A double-blinded RCT in 2006, which included 63,225 patients 2 to 4 months old from 11 Latin American countries and Finland, examined the effect of rotavirus immunization on RG.¹ Infants were randomized to 2 oral doses of rotavirus vaccine or placebo and followed for 9 to 10 months. The primary outcome for the study was the incidence of severe and very severe RG (defined as Vesikari score [VS] 11–18 and ≥ 19 , respectively).

There were 2.0 versus 13.3 children per 1,000 infant-years in the vaccine group and placebo groups, respectively, with at least 1 episode of severe RG ($P < .001$). Efficacy of vaccine against severe RG was 84.7% (95% CI, 71.7–92.4), with 100% efficacy (95% CI, 75.5–100) for very severe RG. Rotavirus immunization compared with placebo did not reduce all-cause mortality (56/10,000 vs 43/10,000 infants; $P = .20$). Mortality was from diarrhea in 2 children from the placebo group and 4 children from the vaccine group, but the etiology of the diarrhea was unknown.¹

A double-blinded RCT in 2010, which included 4,417 infants 6 weeks old from South Africa and Malawi, examined the effect of rotavirus immunization against severe RG (VS > 10).² The patients were randomized to 3 doses of oral rotavirus vaccine, 2 oral doses of rotavirus vaccine plus 1 dose of placebo, or 3 doses of placebo, and followed until 1 year of age.

In South Africa, severe RG occurred in 1.2 versus 5.4 per 100 infant-years in pooled vaccine groups and the placebo group, respectively (rate difference [RD] 4.2%; 95% CI, 2.4–6.5). This translated to an oral vaccine efficacy against severe RG of 76.9%. In Malawi, severe RG occurred in 6.5 versus 13.1 per 100 infant-years in the pooled vaccine groups and the placebo group, respectively (RD 6.7%; 95% CI, 2.4–12). This translated to a vaccine efficacy

against severe RG of 49.4%. Overall efficacy against severe RG was 61.2%. Mortality was not analyzed in this study.²

A double-blinded RCT in 2010, which included 1,969 patients 4 to 12 weeks of age from Bangladesh and Vietnam, examined the efficacy of rotavirus immunization.³ The patients were randomized to 3 oral doses of rotavirus or placebo and followed for a median of 514 days after the last dose.

The incidence of severe RG in the vaccine and placebo groups, respectively, was 3.2 and 6.1 per 100 person-years ($P = .005$); the incidence of all RG was 5.5 and 9.5 per 100 person-years (P value not given). Efficacy of vaccine against RG of any severity was found to be 42.5% (95% CI, 21.1–58.4), 48% against severe RG (VS > 10 ; 95% CI, 22.3–66.1), and 70% against very severe RG (VS ≥ 15 ; 95% CI, 31.8–88.3). Mortality was not analyzed in this study.³

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Are falls in the elderly less common in nursing homes compared with living at home?

EVIDENCE-BASED ANSWER

No. Older adults in nursing homes fall at about twice the rate of age-matched cohorts in the community (SOR: **B**, systematic review and individual prospective cohort studies). Most likely, many confounding variables other than age and place of residence affect fall rate.

A 2002 systematic review of 26 prospective cohort studies studied the rate and risk factors of falls and syncope in a general sample of the elderly population.¹ Using patient and staff surveys, the incidence of falls and self-reported risk factors such as age-related physiologic changes and clinical diseases were reported for age-matched elderly in the community and nursing homes.

CONTINUED

The review found an average of 0.7 falls per person annually in the community (n=6,240; range 0.2–1.6) versus 1.6 falls per person annually in the nursing home (n=4,350; range 0.2–3.6).¹

In a 1995 population-based study, the incidence rate of falls was recorded over a 2-year period using self-report surveys and phone surveys in the home-dwelling elderly (n=1,016) and the nursing home elderly (n=143) 70 years old and older.² In home-dwelling individuals, the incidence of falls was 364 per 1,000 person-years (95% CI, 320–412) for men and 600 per 1,000 person-years (95% CI, 556–647) for women. In long-term care, the corresponding incidence rates were 1,673 per 1,000 person-years (95% CI, 1,388–2,040) for men and 1,406 per 1,000 person-years (95% CI, 1,250–1,581) for women. The confidence intervals for home-dwelling and nursing home elderly did not overlap. Underreporting of falls for home-dwelling elderly may have falsely decreased the incidence of falls at home.

A 1989 prospective cohort study attempted to identify and rank risk factors for falls among nursing home elderly and home-dwelling elderly.³ Patients were matched for age, sex, and living location. During a 12-month period, 373 (53%) of 704 residents living at a nursing home fell at least once, while only 213 (28%) of 761 elderly reported falls in the outpatient setting. Statistical analysis of this difference was not reported.

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Is sleep deprivation associated with behavioral changes in children and adolescents?

EVIDENCE-BASED ANSWER

Reported short sleep duration (≤ 5 hours per night) is associated with suicidality and risky behaviors such as drug use, fighting, weapon carrying, distracted driving, and alcohol consumption. Less than average reported sleep duration is associated with depressive symptoms. Insomnia in children is associated with psychiatric disorders including depression, anxiety, and aggression (SOR: **B**, cross-sectional study and retrospective studies). These associations do not prove causation.

A 2014 cross-sectional study surveyed 15,364 public and private high school students across the United States about their sleep, health, and behaviors.¹ Students were asked about average number of hours slept on a school night and about 12 negative behaviors or conditions: drunk driving, weapon carrying, fighting, suicidal ideation, attempted suicide, smoking, drinking alcohol, binge drinking, marijuana use, sexual risk-taking, texting while driving, and obesity. A significant percentage (29%) of the students reported severe depressive symptoms in the past year.

For sleep on a school night, 31% of students reported 8 hours of sleep, 30% reported 7 hours, 22% reported 6 hours, 11% reported 5 hours, and 7% reported fewer than 5 hours. Getting 7 hours of sleep (8 hours used as a reference) was associated with smoking (odds ratio [OR] 1.2; 95% CI, 1.1–1.4), alcohol use (OR 1.2; 95% CI, 1.1–1.4), binge drinking (OR 1.3; 95% CI, 1.1–1.6), marijuana use (OR 1.2; 95% CI, 1.0–1.4), and texting while driving (OR 1.2; 95% CI, 1.1–1.4). Getting less than 5 hours of sleep was associated with all 12 negative outcomes: drunk driving (OR 2.3; 95% CI, 1.7–3.3), weapon carrying (OR 2.7; 95% CI, 2.1–3.5), fighting (OR 2.4; 95% CI, 1.8–3.1), contemplating suicide (OR 2.5; 95% CI, 2.0–3.2), attempting suicide (OR 2.7; 95% CI, 1.9–3.7), smoking (OR 2.6; 95% CI, 2.0–3.3), alcohol use (OR 1.7; 95% CI, 1.3–2.2), binge drinking (OR 2.5; 95% CI, 2.0–3.1), marijuana use (OR 1.9; 95% CI, 1.5–2.5), sexual risk taking (OR 2.0; 95% CI, 1.4–2.7), texting while driving (OR 1.4; 95% CI, 1.1–1.8), and obesity (OR 1.8; 95% CI, 1.4–2.4).¹

EVIDENCE-BASED PRACTICE LEARNING OBJECTIVES

- 1** To become knowledgeable about evidence-based solutions to commonly encountered clinical problems.
- 2** To understand how ground-breaking research is changing the practice of family medicine.
- 3** To become conversant with balanced appraisals of drugs that are marketed to physicians and consumers.

A 2010 retrospective study of 9th to 11th graders (N=242) evaluated the association among sleep duration, risky behaviors, and depression.² Weekday and weekend sleep durations were calculated using a self-reported survey. Students answered questions about unexcused school absences, alcohol consumption, tobacco and marijuana use in the past month, and depressive symptoms in the past year using the Kandel-Davies scale. This 6-item scale assesses the extent to which depressive and hopelessness symptoms bother the adolescent and has a score of 60 points, with the mean score for a clinical adolescent sample of 21.8. Average weekday sleep duration for the sample was 7.7 hours, with 9.3 hours for weekend sleep.

Increased average weekday sleep (>7.7 hours) was associated with decreased alcohol use and drunkenness (OR 0.71; 95% CI, 0.51–0.99 and OR 0.60; 95% CI, 0.36–0.97, respectively). Current or ever smoking, past month marijuana use, and school absences were not associated with weekday sleep duration. Decreased average weekday sleep (<7.7 hours) was associated with increased depressive symptoms on the Kandel-Davies scale, but numerical results were not reported. No significant associations were noted with weekend sleep duration and any outcome.²

A 2004 retrospective study of 46 children (aged 5–16 years) with sleep disorders presenting to a sleep medicine center examined the frequency and nature of psychiatric symptoms in children referred for insomnia.³ Parents completed questionnaires including a sleep habit questionnaire, the Behavior-Assessment System for Children (BASC) questionnaire, the Pediatric Symptom Checklist (PSC) for correlation with psychiatric disorders, and the Clinical Attention Problem Scale (CAPS) for ADHD diagnosis. Overnight polysomnography was performed for accurate sleep disorder diagnosis as well as measuring sleep latency, sleep efficiency, REM latency, and percentage of REM sleep. Half of the children had a previously diagnosed psychiatric illness (14 children with ADHD, 15 with anxiety, and 7 with mood disorders). Eight of the remaining 23 patients were subsequently diagnosed with depression, anxiety, and aggression.

Adaptability subscores of the BASC and sleep latency were negatively correlated ($r=-0.62$; $P=.02$). Depression (diagnosed by the BASC and evaluating psychiatrist) was positively correlated with sleep latency ($r=0.53$; $P=.04$). Correlation coefficients (r) between 0.5 and 0.7 are considered moderate to strong associations. Of note, 22 of the 23 children without

a preexisting psychiatric illness were on bronchodilators, which can affect sleep.³

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What is the rate of venous thromboembolism (VTE) in women taking combined oral contraceptives (COCs)?

EVIDENCE-BASED ANSWER

The rate of VTE in women taking COCs is approximately 0.06% per year. Third-generation and newer progestins (norgestimate, desogestrel, gestodene, drospirenone, and cyproterone acetate) are associated with greater risk of VTE (about 0.1% per year) (SOR: **B**, consistent findings from cohort studies).

A 2013 retrospective cohort study in California, Tennessee and Washington evaluated the risk of VTE in 835,826 women 10 to 55 years old using multiple formulations and routes of combined hormonal contraception (81,459 were using nonoral routes).¹ Electronic prescription records and coding databases were used to identify exposure to hormonal contraception and outcomes of interest (inpatient and outpatient VTE). Medical records were requested for women who experienced an adverse outcome. Women with VTE in the prior 6 months or those diagnosed with a life-threatening disease were excluded, as were VTE cases with another causative risk factor such as pregnancy or trauma. Women were also dropped from the analysis when documentation was inadequate to exclude other causes of VTE.

The number of VTEs among all contraceptive users was 541 (0.06% per year). The study was limited by the lack of information on confounding factors such as obesity and

family history, as well as the reliance on pharmacy records to identify contraceptive prescriptions without confirming contraceptive use.¹

A 2014 retrospective cohort study of 68,168 German gynecology patients evaluated VTE rates of second-generation and newer COCs over the first year of use.² Data were obtained from the national computer system used by primary care gynecology clinics and included women aged 16 to 45 years with a COC prescription and at least 1 year of follow-up. Women with a prior confirmed diagnosis of thrombosis were excluded.

For all COC users combined, the VTE rate was 0.06% (38 events in 68,168 women) during the first year after initial prescription. This study was limited in that the data were obtained only from gynecology records and if a VTE was not reported by the gynecologist, the event would have been missed.²

A 2013 systematic review and meta-analysis of 25 cohort and case-control studies evaluated VTE risk associated with hormonal contraceptives, paying particular attention to third-generation and newer progestins (norgestimate, desogestrel, and gestodene).³ Approximately 1.8 million patients recruited from 1986 to 2009 were included from multiple countries across Europe and North America.

Third-generation COCs were associated with increased VTE rates versus the second-generation progestins norgestrel and levonorgestrel (11 studies, patient number not given; OR 1.7; 95% CI 1.4–2.0). Drospirenone (8 studies, n=1,765,671; OR 1.7; 95% CI 1.4–2.2) and cyproterone acetate (7 studies, n=1,307,372; OR 1.8; 95% CI 1.4–2.3) were also individually associated with increased odds of VTE versus second-generation progestins. There was statistically significant heterogeneity between studies.³

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Does barefoot running decrease the risk of injuries in runners?

EVIDENCE-BASED ANSWER

There is insufficient patient-oriented evidence to determine if barefoot running decreases the total number of injuries in runners. Barefoot running is associated with mechanical changes that decrease stress on the knee, but increase stress on the ankle (SOR: **C**, meta-analysis of observational studies using disease-oriented outcomes). Traditional shoe runners report higher rates of lower extremity injuries than minimalist shoe runners (SOR: **C**, online survey).

A 2013 systematic review and meta-analysis of 18 nonrandomized observational studies (N=342) evaluated the biomechanical differences of barefoot versus shoe running.¹ All patients were injury-free, long-distance (≥5 km) competitive or recreational adult runners. Their biomechanics were measured while running with their personal shoe, racing flats, or minimalist shoes.

The pooled analysis showed that barefoot running was associated with decreased ground reaction force, reduced foot and ankle dorsiflexion, and increased knee flexion (see **TABLE 1**). A qualitative summary for outcomes in which pooling was not possible concluded that barefoot running was associated with shorter stride length, increased stride frequency, decreased knee extension, and greater power absorption to the ankle. All of the studies were of low methodological quality based on modified Downs and Black quality index scores (<16 of 21 points).¹

A 2012 anonymous online survey (N=904) investigated the association between injury and the wear of traditional shoes, minimalist shoes, or barefoot running.² The survey was sent to email distribution lists of local, military, and university running clubs. Only 16 experienced barefoot runners responded (defined as individuals who had not changed footstrike pattern in the past year and had been running barefoot >50% of their running career). The barefoot runners had an average age of 37 years, 12 years of running experience, and 75% were male. The minimalist runners had an average age of 39 years, 9 years of running experience, and 69% were male. The

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TABLE 1

Biomechanical changes with barefoot versus shod running¹

Outcome	Studies	N	Effect size	95% CI
Peak vertical ground reaction force	5	176	-0.47	-0.77 to -0.17
Vertical impact ground reaction force	3	104	-0.82	-1.2 to -0.41
Foot dorsiflexion at ground impact	4	66	-0.18	-2.4 to -1.2
Ankle dorsiflexion at ground impact	6	134	-1.3	-1.8 to -0.92
Knee flexion at ground impact	5	118	0.49	0.12 to 0.87

Note: An effect size of magnitude 0.2 is considered small, 0.6 moderate, 1.2 large, and 2.0 very large.

TABLE 2

Self-reported injury rates by shoe type²

Anatomical region	Self-reported injury rates (%)		P
	Traditional shoes	Minimalist shoes	
Any injury	47	14	<.001
Foot	14	5.3	.001
Ankle	8.8	3.1	.007
Lower leg	12.7	4	<.001
Knee	17.1	5.3	<.001
Thigh	3.2	1.8	NR
Hip	8.8	0.9	<.001
Low back	3.3	0.5	NR

Barefoot runners not included due to limited sample size.

NR=not reported.

traditional shoe runners had an average age of 37 years, 6 years of running experience, and 43% were male. Runners were asked to describe their foot strike pattern, shoe preference, running habits, and injury history (defined as an event of discomfort or pain altering the training schedule longer than 1 week with or without a medical visit).

Forefoot strike pattern was associated with the lowest risk of an injury history (n=881; 52% rearfoot, 35% midfoot, and 23% forefoot; $P<.001$) and minimalist shoes were also associated with lower injury rates than traditional shoes (see **TABLE 2**). Increased running experience correlated with lower injury rates (55% for 1–5 years, 49% with 6–10 years, 43% for >10 years; $P=.046$). Weekly mileage

was not correlated with injury rates when running more than 30 miles per week was compared with running less than 20 miles per week (41% vs 36%; $P=.16$).²

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In patients with type 2 diabetes, does regular fruit consumption lead to poorer glycemic control than patients who eat a low-fruit diet?

EVIDENCE-BASED ANSWER

No. In patients with new-onset type 2 diabetes and an hemoglobin A1C (HbA1C) <7%, higher whole and fresh fruit consumption does not worsen short-term (12 weeks) glycemic control (SOR: **C**, single RCT of disease-oriented outcomes). Higher consumption (2 servings per day) of low-calorie whole fruits may improve glycemic control in patients with an HbA1C of 8% (SOR: **C**, single RCT of disease-oriented outcomes).

A 2013 Danish open RCT (N=63) of adult patients with newly diagnosed type 2 diabetes and HbA1C <7% assessed the effect of medical nutrition therapy plus high-fruit diet (≥ 2 pieces of fruit per day) versus medical nutrition therapy plus low-fruit diet (≤ 2 pieces of fruit per day) on HbA1C.¹ Fruit was whole or fresh; no canned, dried, or juices were consumed. Patients recalled fruit consumption and researchers converted into grams based on a standard table with pictures (eg, 1 apple=100 g). Participants who adhered to the high-fruit diet consumed an average of 319 g/d (125-g increase from baseline) and those on the low-fruit diet ate 135 g/d (51-g decrease from baseline).

Both groups had lower HbA1C, but after 12 weeks the mean difference in HbA1C between the groups was not significant (mean difference 0.19%; 95% CI, -0.23% to 0.62%).¹

A 2013 RCT (N=123) from India of adult patients 40 to 75 years old with type 2 diabetes assessed the effect of standard medical nutrition therapy (including ≤ 1 serving of fruit per day) versus higher fruit consumption (an increase of 2 servings of fruit per day in addition to medical nutrition therapy) on HbA1C and fasting plasma glucose.² Baseline HbA1C in both groups was 8.0%. Fruits were low-calorie and available throughout the year. One serving of fruit consisted of 1 sweet lime, 1 orange, 1 apple, or 10 slices of papaya.

After 12 weeks, the higher fruit consumption group had a 0.3% decrease in HbA1C ($P<.001$) and 0.7 mmol/L decrease in fasting plasma glucose ($P<.001$) from baseline. The standard diet group had a 0.5% increase in HbA1C ($P<.001$) and

0.4 mmol/L increase in fasting plasma glucose ($P<.001$) from baseline.²

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What dose of thiamine should be used for prevention of Wernicke's encephalopathy?

EVIDENCE-BASED ANSWER

No consensus exists regarding the specific dose of thiamine that should be given for prevention of Wernicke's encephalopathy. Surrogate outcome measures for prevention of Wernicke-Korsakoff syndrome suggest 200 mg intramuscularly (IM) daily for 2 days is better than 5 mg IM for 2 days (SOR: **B**, RCT). It is recommended that more than 25 mg/d should be given parentally for at least 5 days followed by oral therapy (SOR: **C**, consensus guideline).

A 2013 systematic review of thiamine for prevention of Wernicke-Korsakoff syndrome (WKS) in people at risk from alcohol abuse included 2 RCTs (N=177), but only 1 had data to do an analysis.¹ The larger study (n=169) evaluated patients with history of heavy alcohol use for a mean of 17 years admitted for alcohol detoxification, but without symptoms of WKS. Patients were randomized to receive 5, 20, 50, 100, or 200 mg thiamine IM once per day for 2 consecutive days. The only outcome measure was a delay in alternation testing results, in which the patient was instructed to find a coin that would be placed under 1 of 2 covers. Once found, the coin was placed under the other cover where it would stay until found, and so on.

Improvement in the number of trials taken to recognize the pattern and reach the criterion of 12 correct consecutive responses was statistically significant for the 200 mg/d dose

compared with the 5 mg/d dose (mean difference [MD] −18; 95% CI, −35 to −0.40). No significant differences were noted when comparing 5 mg with the other doses, suggesting no linear dose–response relationship.¹

A 2010 evidence-based guideline from the National Clinical Guideline Centre at the Royal College of Physicians reviewed multiple studies on Wernicke’s encephalopathy, including the RCT from the systematic review above.² The other studies included RCTs and observational studies comparing routes of administration and not doses. The guideline recommended doses of more than 25 mg/d and the parenteral route for a minimum of 5 days followed by oral therapy (no level of evidence indicator).

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Which oral contraceptives are more effective for the treatment of adult acne in females?

EVIDENCE-BASED ANSWER

Combined oral contraceptives (COCs) improve acne compared with placebo. COCs with drospirenone appear to decrease total lesion counts slightly more than COCs with norgestimate and are 84% less likely to be associated with acne deterioration than COCs with levonorgestrel. There do not appear to be differences in the comparative effectiveness in treating acne of COCs containing levonorgestrel versus norethindrone acetate and desogestrel versus norgestimate (SOR: **B**, systemic review of RCTs and single RCT without specific recommendation).

A 2012 systematic review of 31 RCTs (N=12,579) examined the efficacy of COCs for the treatment of facial acne.¹ Only

17 of these trials compared COCs with each other and, within these trials, only 6 compared COCs available in the United States. The studies varied with regard to sample size (24–2,152 patients) and duration (3–13 months). Included progestins available in the United States were desogestrel (DSG), dienogest drospirenone (DRSP), levonorgestrel (LNG), norethindrone acetate (NA), and norgestimate (NGM). Most were combined with ethinyl estradiol (EE) 20 to 50 µg, but 1 trial used 17β-estradiol 1.5 mg.

Although 9 placebo-controlled trials (with 4,614 patients 14–49 years old) found COCs with various progestins were effective in reducing acne lesion counts, severity grades, and/or self-assessed acne compared with placebo, direct comparisons of COCs were limited and yielded inconsistent results.¹

Two trials compared DRSP/EE to other COCs.¹ One trial (n=1,154) compared DRSP 3 mg/EE 30 µg with triphasic NGM 180-215-250 µg/EE 35 µg. The DRSP group had a greater mean percentage decrease in total lesion count after cycle 6 (mean difference −3.3%; 95% CI, −6.5 to −0.15). The second trial (n=424) comparing DRSP 3 mg/EE 30 µg with LNG 150 µg/EE 30 µg found the DRSP group was less likely to discontinue due to acne deterioration (odds ratio [OR] 0.16; 95% CI, 0.05–0.47). LNG/EE was compared with DSG/EE in 3 trials. Two trials (n=88) compared LNG 150 µg/EE 30 µg with DSG 150 µg/EE 30 µg. While 1 trial found a difference in mean acne severity score on a 4-point scale (mean difference 0.50; 95% CI, 0.09–0.91) favoring the DSG group, the second trial showed the differences in mean total lesion count were not significantly different between the groups. The third trial (n=1,027) compared LNG 100 µg EE 20 µg with DSG 150 µg/EE 20 µg. At 25 weeks, the DSG group was more likely than the LNG group to show improvement in comedones (OR 1.6; 95% CI, 1.0–2.3) and less likely to have worsening of papules (OR 0.60; 95% CI, 0.37–0.96). One multicenter trial (n=58) compared LNG 100 µg/EE 20 µg with NA 1 mg/EE 20 µg and found a nonsignificant difference in mean change in total lesion count.

A 2014 RCT compared EE with NGM to EE with DSG for the treatment of mild to moderate acne.² Healthy women between 18 and 45 years old with mild to moderate acne vulgaris were randomized to triphasic EE/NGM or biphasic EE/DSG and treated for 6 cycles. A total of 201 women completed the study. Patients were evaluated for efficacy during 3 treatment visits after 1, 3, and 6 months by lesion

count including comedones, papules, pustules, and nodules. The study found no differences between formulations for the mean percentage decrease in total acne lesion counts (74.4% vs 65.1%, respectively; $P=.07$) or facial acne improvement score. The 5-point facial improvement score was assessed by investigators as excellent, good, fair, no change, and worse and by patients as much improved, somewhat improved, not improved, worse, and much worse.²

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What symptoms and risk factors predict pathological GERD in infants?

EVIDENCE-BASED ANSWER

Infants who reflux more than 5 times a day are more likely to have pathological gastroesophageal reflux disease (GERD), although the positive predictive value is only 29% (SOR: **C**, moderate and low-quality evidence from observational studies). Symptoms such as persistent crying, back arching, hiccups, coughing, and vomitus volume do not correlate with abnormal esophageal pH or esophagitis on biopsy. Pneumonia, apnea with fussing, and defecation less than once a day are associated with abnormal esophageal pH (SOR: **C**, moderate quality evidence from observational studies).

A 2006 Australian prospective cohort study investigated 151 infants admitted for persistent distress (mean age 2.5 months, range 0.5–8.2 months, 54% male).¹ A 24-hour cry/fuss chart was completed on hospital day 1 and the infants all underwent 24-hour esophageal pH monitoring. The authors defined GERD as fractional reflux time (FRT) of more than 10% with esophageal pH less than 4. Overall, 18% of patients had GERD.

Infants with more than 5 episodes of regurgitation daily had an increased risk of GERD compared with infants who did not have more than 5 episodes of regurgitation daily (odds

ratio [OR] 2.9; 95% CI, 1.1–7.4); however, the positive predictive value for GERD was only 29%. GERD was not associated with infant age, crying duration, volume of regurgitation, back arching, or breast or formula feeding.¹

In a 2005 case-control Belgian study, investigators compared 100 infants referred because of symptoms of suspected GERD with 100 well-baby controls (0.5–12 months old, median age 4 months).² Parents filled out a symptom questionnaire assessing such symptoms as frequency and volume of vomiting, duration of crying, crying during feeds, refusing to feed, weight gain, pneumonia, bronchitis, hiccups, diarrhea, constipation, and family history of reflux or allergies. All 100 infants with suspected GERD underwent esophageal pH monitoring and all were offered upper endoscopy and biopsy, but only 44 parents consented.

Infants in the suspected GERD group had significantly more reported episodes of spitting up (68% vs 45% in the well-baby group; $P<.05$) and crying more than 1 h/d (51% vs 20%; $P<.01$) than the well babies. Among the suspected GERD infants who had pH studies, 21% were positive for GERD (FRT >10%, pH <4.0). Abnormal pH was significantly associated with pneumonia or apnea with fussing ($P=.01$ for both), defecation less than once a day ($P=.03$), and constipation ($P=.05$). Of the 44 infants who had esophageal biopsy, 17 (39%) had histologic evidence of esophagitis. The symptom questionnaire correlated poorly with GERD or esophagitis: 81% of babies with both normal pH and biopsies had positive scores on the questionnaire while 29% of babies with abnormal biopsies and 19% with abnormal esophageal pH had negative questionnaires.²

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In patients with type 2 diabetes who are maximized on metformin with HbA1C above 7%, are GLP-1 agonists more effective than sulfonylureas for lowering HbA1C?

Bottom line

There is no convincing evidence that glucagon-like peptide-1 (GLP-1) agonists are more effective than sulfonylureas for lowering hemoglobin A1C (HbA1C) when added to metformin therapy (SOR: **B**, based on 2 meta-analyses with conflicting results).

Evidence summary

In 2014, a meta-analysis of 277 RCTs compared various drug regimens for lowering HbA1C, such as metformin monotherapy versus metformin plus GLP-1 agonists, and metformin monotherapy versus metformin plus sulfonylureas.¹ The dosages and lengths of treatment were not documented.

Compared with metformin monotherapy, metformin plus GLP-1 agonists were more likely to achieve target HbA1C (1 trial, n= 64; odds ratio [OR] 11; 95% CI, 3.4–36). Similarly, metformin plus sulfonylureas were more likely to achieve target HbA1C than metformin alone (7 trials, n=1,232; OR 4.1; 95% CI, 3.0–5.5). However, the only head-to-head study referenced in this meta-analysis that compared metformin plus GLP-1 agonists with metformin plus sulfonylureas for achieving target HbA1C showed no significant difference (1 trial, n=465; OR 1.0; 95% CI, 0.71–1.5).¹

In 2011, a systematic review and meta-analysis of 40 RCTs compared the efficacy of various antihyperglycemic therapies in lowering HbA1C when added on to metformin in 17,795 patients with type 2 diabetes inadequately controlled by metformin monotherapy.² The HbA1C was lower in the metformin plus sulfonylurea group than the metformin monotherapy group (3 trials, n=1,874; weighted mean difference [WMD] –0.80%; 95% CI, –1.0 to –0.59). Similarly, the HbA1C was lower for the metformin plus GLP-1 agonist group than the metformin monotherapy group (4 trials, n=1,727; WMD –0.75%; 95% CI, –0.96 to –0.53). No direct comparisons were made between metformin plus sulfonylureas versus metformin plus GLP-1 agonists.

It was noted that weight gain was more likely with the addition of sulfonylureas to metformin compared to

metformin alone (3 trials, n=927; WMD 1.79 kg; 95% CI, 1.3–2.3) than with the addition of GLP-1 agonists to metformin compared to metformin alone (2 trials, n=480; WMD –1.6 kg, 95% CI, –3.5 to 0.37).²

Recommendations from others

The Canadian Agency for Drugs and Technologies in Health (CADTH) released an updated evidence-based guideline in 2013.³ They recommended that a sulfonylurea be added to metformin for most adults with type 2 diabetes inadequately controlled on metformin alone because it is the most cost-effective treatment option, and has considerably more long-term safety data than drugs from newer classes of antihyperglycemic agents (Quality of Evidence: level I, high, based on a systemic review of 69 RCTs).

Their economic analysis suggested that the cost of GLP-1 agonists would have to be lower by 95% in order to be more cost-effective than sulfonylureas as a second-line antihyperglycemic option.³

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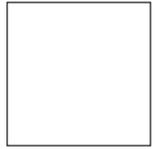
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What is the best initial treatment for an adult diagnosed with ADHD?

EVIDENCE-BASED ANSWER

Treatment with psychostimulant medications such as methylphenidate and amphetamine derivatives moderately improve short-term symptom severity compared with placebo in adults with attention deficit hyperactivity disorder (ADHD) and should be used as initial pharmacological treatment (SOR: **A**, meta-analyses of RCTs and evidence-based guideline).

A 2011 meta-analysis included 7 RCTs evaluating amphetamines versus placebo or nonamphetamine active intervention for treatment of ADHD in adults (N=1,091; mean study length 8 weeks).¹ Patients were diagnosed by any standardized criteria and trials were not limited to initial treatment. Studies measured symptom severity using different scales, so pooled results were reported as a standardized mean difference (SMD).

Amphetamines (dextroamphetamine 10.2–21.8 mg/d, lisdexamfetamine 30–70 mg/d, and mixed amphetamine salts [MAS] 20–60 mg/d), independent of dose and release formulation, moderately improved short-term ADHD symptom severity compared with placebo in all trials (SMD -0.72; 95% CI, -0.87 to -0.57). Patients treated with amphetamines reported no difference in symptom severity compared with nonamphetamine drug interventions: guanfacine 0.25–2 mg/d (1 trial, n=34; SMD 0.18; 95% CI, -0.35 to 0.71), modafinil 50–200 mg/d, titrated as tolerated to maximum dose of 200 mg/d (1 trial, n=44; SMD 0.11; 95% CI, -0.26 to 0.48), and paroxetine 20 mg/d titrated as tolerated to maximum dose of 40 mg/d (1 trial, n=49; SMD -0.40; 95% CI, -0.97 to 0.16).¹

A 2009 meta-analysis included 12 double-blind parallel-group RCTs comparing stimulants dosed daily (methylphenidate 0.9–1.1 mg/kg, mixed amphetamine salts 20–60 mg, dexamethylphenidate 20–40 mg, and lisdexamfetamine 30–70 mg) and nonstimulant medications dosed daily (bupropion 300–362 mg, bupropion XL 393 mg, atomoxetine 120 mg, and desipramine 200 mg) with placebo for treatment of ADHD in adults (N=1,991).² Duration of trials ranged from 4 to 10 weeks.

The pooled effect size across all treatments in the trials compared with placebo was in the medium range (SMD 0.65; 95% CI, 0.48–0.81). The effect size for stimulants (7 trials, n=1,102; SMD 0.67; 95% CI, 0.36–0.97) was higher than for nonstimulant medications (6 trials, n=800; SMD 0.59; 95% CI, 0.37–0.81). However, the appearance of superiority was based on separate studies rather than head-to-head comparisons.²

In 2014, the British Association for Psychopharmacology published an update on evidence-based guidelines that included the pharmacological management of ADHD and recommended stimulant medications, such as amphetamines and amphetamine derivatives, as initial therapy in adults (level I evidence from meta-analysis, systematic reviews, and RCTs).³

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In transgender men (female-to-male), are long-acting testosterone injections an effective masculinizing therapy?

EVIDENCE-BASED ANSWER

Yes. Long-acting testosterone injections are an effective masculinizing therapy as determined by patient satisfaction and time to amenorrhea for transgender men (SOR: **B**, lower-quality individual RCT). Long-acting testosterone injections also increase lean muscle mass, facial hair, and sexual desire (SOR: **C**, lower-quality prospective observational studies).

In a 2014 RCT, transgender men (N=45) were assigned to long-acting testosterone undecanoate intramuscular (IM) injections (1,000 mg every 6 weeks for the first 2 shots, then every 12 weeks), short-acting testosterone Testoviron depot IM injections (100 mg every 10 days), or transdermal testosterone gel (T-gel) (50 mg applied daily) to compare the difference in effects among formulations.¹ Patients were studied at baseline, 30 weeks, and 54 weeks, and an ANOVA multivariate analysis was performed to accommodate comparisons among more than 2 groups (2-tailed *P* values <.05 used to denote significance).

No significant difference was noted among the groups in time to amenorrhea (Testoviron depot 30 weeks, T-gel 40 weeks, testosterone undecanoate 41 weeks). Mean serum testosterone did not vary significantly among the 3 groups at any time. In all patients and groups, mean total testosterone values were substantially below the normal male range at baseline and increased to the normal male range at both 30 and 54 weeks. Satisfaction was assessed at baseline and at 54 weeks using a 10-point visual analog scale (VAS), and patients in the different treatment arms reported no significant difference in satisfaction. The VAS ranks satisfaction from 0 (“greatest dissatisfaction”) to 10 (“greatest satisfaction”), and patients in all treatment arms were reported as “highly satisfied,” although the results were presented graphically.¹

A 2-year prospective observational study with a focus on body composition and bone mineral density followed transgender men (N=45) who were given 1,000 mg long-

acting testosterone undecanoate IM injections every 12 weeks.² Total testosterone levels and amenorrhea were secondary outcomes.

Comparing lean body mass at 12 and 24 months with baseline, patients demonstrated a significant increase in lean body mass of 1.7 kg at 12 months (*P*=.01 vs baseline) and 1.9 kg at 24 months (*P*≤.01 vs baseline). Total testosterone increased from a mean of 40 ng/dL at baseline to 691 ng/dL at 12 months (*P*<.0001) and 605 ng/dL at 24 months (*P*<.0001). All patients reported 1 additional menstrual bleed after beginning their injections, followed by amenorrhea.²

This study was limited by the small size of the population, and lack of standardization between subjects with regard to exercise, smoking, alcohol consumption, and diet, all of which play a role in body composition.²

A 1-year prospective observational study of transgender men (N=53) evaluated hormonal changes and desired clinical changes (including lean muscle mass, voice deepening/instability, and facial hair) occurring with long-acting testosterone therapy.³ Patients received 1,000 mg long-acting testosterone IM injections every 6 weeks for the first 2 shots then every 12 weeks.

All patients achieved serum total testosterone levels in the male reference range of 321–1,005 ng/dL, with a baseline mean of 30 ng/dL and elevation to a mean of 596 ng/dL at 12 months (*P*<.001). At 12 months, lean muscle mass increased by an average of 5.3 kg compared with baseline (*P*<.001). Voice deepening/instability was reported by 60% of patients at 12 months compared with baseline measurements (*P*=.024) and facial hair increased from a baseline of 0 to 10 (maximum score 36) at 12 months using the Ferriman Gallwey hirsutism scoring system (*P*<.001). This system assesses the presence of hair growth at 19 locations, with a score of more than 9 indicating androgen excess in women.³

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What is the best initial antibiotic regimen for patients hospitalized with an MRSA cellulitis?

EVIDENCE-BASED ANSWER

The answer is not entirely clear. However, for methicillin-resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infections (SSTIs), linezolid has a higher clinical cure rate and decreased length of stay than vancomycin (SOR: **A**, systematic review of RCTs). Daptomycin is associated with faster clinical resolution and fewer days of inpatient therapy than vancomycin in patients with SSTIs and risk factors for MRSA (SOR: **B**, cohort study). Vancomycin, linezolid, daptomycin, telavancin, and clindamycin are all acceptable antibiotic regimens for patients hospitalized with MRSA cellulitis (SOR: **C**, expert consensus).

A 2013 Cochrane review of 9 RCTs (N=3,144) compared linezolid 600 mg every 12 hours (either oral or intravenous) with intravenous vancomycin 1,000 mg every 12 hours for treatment of SSTIs.¹ In a subset analysis of 5 trials with patients aged 13 years and older hospitalized for infections due to MRSA (n=2,659), linezolid was significantly better in clinical cure rates (relative risk [RR] 1.1; 95% CI, 1.0–1.2) as defined by complete resolution of pretherapy signs and symptoms. No significant difference was noted in all-cause mortality between linezolid and vancomycin (RR 1.44, 95% CI, 0.75–2.80). Four of the 5 RCTs reported duration of hospital stay in mean number of days, with all 4 showing shorter duration with linezolid than vancomycin, by 2 to 5 days. These 5 trials were at high risk of bias due to lack of blinding and allocation concealment, and also having been funded by the pharmaceutical company that manufactures linezolid.

A 2007 cohort study (N=265) evaluated intravenous daptomycin 4 mg/kg every 24 hours for treatment of complicated SSTIs in patients 18 to 85 years old compared with historical controls receiving vancomycin dosed to achieve trough concentrations of 5–20 mcg/mL.² SSTIs were diagnosed in patients having tenderness, erythema, warmth, or discharge plus established risk factors for MRSA cellulitis. A total of 53 patients were treated in the daptomycin arm

for at least 3 days but no more than 14 days. The control group consisted of 212 patients who received vancomycin for at least 3 days and could then be transitioned to oral medications based on historical standard of care.

The percentage of patients with infection resolution—defined as the absence of all preclinical signs and symptoms—on day 3 was 90% versus 70% ($P<.01$) and on day 5 was 98% versus 81% ($P<.01$) in the daptomycin and vancomycin groups, respectively. Total duration of inpatient antibiotic therapy was 4 days in the daptomycin group and 8 days ($P<.05$) in the vancomycin group. All patients reached infection resolution by the end of total therapy in both groups.²

In 2011, the Infectious Diseases Society of America published a guideline on MRSA infections based on the consensus judgment of a technical expert panel after a systematic literature review.³ The guideline recommended that for patients hospitalized with complicated SSTIs (major abscesses, surgical wound infections, or deep soft-tissue infections), empiric treatment for MRSA should be considered. Recommendations for medical therapy are vancomycin IV every 8 to 12 hours, linezolid 600 mg PO or IV twice daily, daptomycin 4 mg/kg/dose IV once daily, telavancin 10 mg/kg/dose IV once daily, or clindamycin 600 mg IV or PO 3 times daily.

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In adults using antibiotics, do high-dose probiotics result in greater reduction of gastrointestinal symptoms than low-dose probiotics?

EVIDENCE-BASED ANSWER

Compared with low-dose probiotics, high-dose probiotics reduce duration of antibiotic-associated diarrhea (AAD) and certain gastrointestinal (GI) side effects associated with antibiotic use, such as fever, abdominal pain, bloating, abdominal distension, loose stools, and constipation (SOR: **B**, RCTs). High-dose probiotics may also reduce incidence of AAD and *Clostridium difficile*-associated diarrhea (CDAD) (SOR: **B**, conflicting RCTs). Data may be biased due to industry sponsorship of trials.

A 2014 single-center, triple-blind, industry-sponsored, RCT in China evaluated the effect of probiotics on GI symptoms in 503 hospitalized adults 30 to 70 years old taking antibiotics (penicillins, cephalosporins, or clindamycin) for 3 to 14 days.¹ Exclusion criteria included pregnancy, breastfeeding, active diarrhea, prior consumption of probiotics or fermented milk products, prior probiotic allergy, uncontrolled intestinal disease, *C difficile* infection within the past 3 months, parenteral nutrition, NPO status, immunosuppressed state, antibiotic use within the past 1 month, and lactose intolerance. Participants were stratified by age, sex, and duration of antibiotic therapy and then randomized to receive HOWARU® Restore 4-strain probiotic formula at a high dose of 17 billion CFU (n=168), a low dose of 4.17 billion CFU (n=168), or placebo (n=167). Probiotics were initiated within 36 hours of antibiotic initiation and continued until 7 days after antibiotic completion. Compliance and GI symptoms were followed during admission and for 4 weeks after discharge.

Compared with the low-dose probiotic group, the high-dose probiotic group had a nonsignificant reduction in incidence of AAD (19.6% vs 12.5%; $P=.08$). The high-dose group had shorter duration of AAD (3.5 vs 2.6 days; $P=.03$) and lower incidence of fever, abdominal pain, and bloating. Incidence of CDAD was not different in the low- and high-dose groups. No adverse effects were attributed to probiotics.¹

A 2010 single-center, triple-blind, industry-sponsored RCT in China evaluated the effect of probiotics on GI

symptoms in 255 hospitalized adults aged 50 to 70 years taking antibiotics (penicillins, cephalosporins, or clindamycin) for 3 to 14 days.² Exclusion criteria included use of other probiotics, active diarrhea, uncontrolled intestinal disease, documented *C difficile* infection within the past 3 months, immunosuppressive therapy, antibiotic use within the past 30 days, or active participation in another clinical study. Participants were stratified by age and duration of antibiotic therapy and then randomized to receive Bio-K + International brand® 3-strain probiotic formula at a high dose of 100 billion CFU (n=86), a low dose of 50 billion CFU (n=85), or placebo (n=84). Probiotics were initiated within 36 hours of antibiotic initiation and continued until 5 days after antibiotic completion. GI symptoms were followed during admission and for 3 weeks after discharge.

Compared with the low-dose probiotic group, the high-dose probiotic group had lower incidence of AAD (28.2% vs 15.5%; $P=.02$), shorter mean duration of AAD (4.1 days vs 2.8 days; $P=.04$), lower incidence of CDAD (9.4% vs 1.2%; $P=.04$), and lower incidence of abdominal pain, abdominal distension, loose stools, and constipation. No adverse effects were attributed to probiotic use.²

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Is capsaicin cream safe and effective at reducing knee osteoarthritis pain?

EVIDENCE-BASED ANSWER

Capsaicin cream and its cis-isomer, civamide, have small to moderate effects reducing osteoarthritis knee pain after at least four weeks of use. Capsaicin cream is safe, but commonly causes application-site burning that rarely leads to stopping treatment (SOR: **A**, systematic review of RCTs and one crossover study).

A 2014 systematic review examined capsaicin cream for knee osteoarthritis in 5 double-blind RCTs and 1 case-crossover trial

including 1,162 patients with average ages 49 to 65 years.¹ Trials assessed treatment efficacy versus placebo over 4 weeks, with 2 studies reporting data beyond 4 weeks. Capsaicin concentrations ranged from 0.025% to 0.075% used topically 3 to 4 times per day. Visual analog scales (VAS) assessed pain, either from 0 to 10 or 0 to 100.

Capsaicin cream reduced VAS pain score with standardized mean difference (SMD) of 0.44 after 4 weeks of treatment (95% CI, 0.25–0.62) compared with placebo (An SMD of 0.2 is considered small, 0.6 moderate, and 1.2 large). Results were consistent across the trials with no heterogeneity. Two trials reported continued effectiveness up to 20 weeks (numerical results not reported). Mild application site burning was the most common reaction reported in 35% to 100% of patients (RR 4.2; 95% CI, 3.3–5.5).¹

A 2012 double-blind RCT compared civamide 0.075% cream (the cis-isomer of capsaicin) with civamide 0.01% (a less active control cream to promote blinding) in reducing osteoarthritis knee pain in 695 patients (aged ≥50).² Pain was assessed with the Western Ontario McMaster University Osteoarthritis Index (WOMAC) at baseline and after 12 weeks of treatment. WOMAC scores for pain range from 0 to 20, with higher numbers representing more pain; a WOMAC score of more than 13 is considered severe pain. Response was defined as at least 50% improvement in either the WOMAC pain or WOMAC function scores, or at least 20% improvement in both.

Among patients whose baseline WOMAC pain scores were more than 10, 68% of civamide 0.075% users responded versus 54% of civamide 0.01% users ($P=.002$). With baseline WOMAC scores more than 13, 78% of civamide 0.075% users responded versus 51% of civamide 0.01% users ($P<.001$). Application site burning was the most common adverse reaction, with only 5% of patients stopping the medication due to this reaction. Adverse reactions decreased as the study went forward—they were recorded for 18% of patients in the treatment arm on day 1, 10% by day 14, and 6% by day 84.²

A 2010 double-blind, randomized, placebo-controlled trial of 100 Thai women 44 to 82 years old with mild to moderate knee osteoarthritis compared 0.0125% capsaicin cream with placebo gel for treatment of knee osteoarthritis pain over 4 weeks.³ Pain was assessed on a VAS (range 0–10), and the WOMAC scores for pain at baseline and after 4 weeks of treatment.

The mean difference in VAS scores with capsaicin versus placebo was 0.72 after 4 weeks of treatment (95% CI, 0.17–1.3). The reduction in mean total WOMAC scores was 3.4 points greater (95% CI, 2.34–4.5) in the capsaicin group than the control group. Application site burning was the only reported adverse event, occurring in 67% of patients in the capsaicin group versus 17% in placebo group. No patients discontinued the medication due to an adverse reaction. This study was limited in that only women farmers were included.³

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Can HbA1C be used to predict which patients are at risk for developing type 2 diabetes mellitus?

EVIDENCE-BASED ANSWER

Glycosylated hemoglobin (HbA1C) 5.3%–6.4% has a similar predictive value to fasting plasma glucose (FPG) >99 mg/dL over 5 to 6 years; an abnormal result on both measures is more predictive of developing type 2 diabetes mellitus (DM2) than an abnormal result on either test alone (SOR: **C**, consistent cohort studies of disease oriented outcomes).

A 2011 longitudinal cohort study of 6,241 Japanese patients (4,670 men, 1,571 women; age range 24–82 years; mean age 49.9 years) with and without prediabetes (HbA1C 5.7%–6.4% and/or impaired FPG 100–124 mg/dL) were assessed annually for the rate of progression to DM2 during a mean 4.7-year follow-up.¹ Patients with preexisting cardiovascular risk factors (ie, smoking history, hypertension, hyperlipidemia, history of coronary heart disease and stroke) were included. Of 2,092 patients with baseline prediabetes, 292 new incident cases of diabetes

were reported in these patients over the course of study period.

The combination of HbA1C and FPG identified more new incident cases of diabetes (46%, n=154; hazard ratio [HR] 32; 95% CI, 23–45) than either FPG (32%, n=108; HR 6.2; 95% CI, 4.3–8.8) or HbA1C (9%, n=30; HR 6.0; 95% CI, 3.8–9.6) alone. Furthermore, 38% of patients with prediabetes by both HbA1C and FPG criteria were diagnosed with diabetes within 5 years, compared with 9% and 7% for either FPG or HbA1C alone.¹

A 2011 prospective cohort study (N=630) assessed the role of HbA1C in predicting DM2 compared with FPG and oral glucose tolerance test (OGTT) in nondiabetic patients (age range 30–75 years) in Spain.² Patients underwent HbA1C, OGTT, fasting and 2-hour venous blood samples (2hPG). There were 44 new cases of DM2 over a mean follow-up of 6.3 years.

DM2 incidence rates increased substantially for patients with baseline HbA1C 5.5%–6.9% (n=31; 33 cases per 1,000 person-years, 95% CI, 23–46) versus HbA1C 3.4%–5.4% (n=13; range 1–7.9 cases per 1,000 person-years). Thresholds for FPG, 2hPG, and HbA1C for predicting diabetes closest to 100% sensitivity and specificity were 100 mg/dL, 120 mg/dL, and 5.5%, respectively. HbA1C, FPG, and 2hPG were all comparable in the prediction of diabetes (receiver operating characteristic areas under the curve [ROC-AUC] for HbA1C 0.80; 95% CI, 0.74–0.86; for FPG 0.83; 95% CI, 0.77–0.90; and for 2hPG 0.79; 95% CI, 0.72–0.87). The combination of FPG and HbA1C had the best predictive performance (ROC-AUC 0.88; 95% CI, 0.82–0.93).²

A 2010 prospective cohort study compared HbA1C and FPG for predicting 5-year incident diabetes in 1,189 Japanese nondiabetic patients (age range 35–89 years).³ HbA1C, FPG, and 2-hour GTT were performed at baseline and a 5-year follow-up.

No statistical difference was noted in sensitivity between FPG 100 mg/dL and HbA1C 5.3% (61% and 56%, respectively; P=NS), while specificity was higher in HbA1C 5.3% than FPG 100 mg/dL (88% vs 83%; P<.001) in diagnosis of DM in 5 years.

A 2006 prospective cohort study examined HbA1C in predicting progression to DM2 in 2,924 French patients (age range 30–65 years) at inclusion and followed 6 years.⁴ Volunteers presented for a routine health check-up, and were excluded for known diabetes, unknown glucose status, or missing HbA1C, waist circumference, or body mass index

information. HbA1C was predictive of DM2 within this cohort only if patients also had a FPG ≥109 mg/dL. Of these patients, patients with HbA1C >5.9% had a 50% risk of progression to DM2 within 6 years. FPG alone did not predict DM2 risk.

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How accurate are rapid diagnostic tests (RDTs) in diagnosing *Plasmodium falciparum* malaria in endemic areas?

EVIDENCE-BASED ANSWER

Single-antigen RDTs for *P falciparum* have a sensitivity ranging from 90% to 95% and a specificity from 90% to 95% and are adequate for use in extending the access of diagnostic services in endemic areas (SOR: **A**, meta-analysis of diagnostic cohort studies). Dual-antigen combination RDT's may increase diagnostic specificity in children (SOR: **B**, diagnostic cohort study).

A 2011 Cochrane review of 74 diagnostic cohort studies (including 111 different test evaluations and 60,396 test results) evaluated the test characteristics of RDTs for the diagnosis of *P falciparum* malaria using microscopic evaluation of Giemsa-stained thick and thin smears as the reference standard.¹ Patients of all ages presenting to ambulatory clinics in *P falciparum* endemic areas with symptoms of uncomplicated malaria were included in the studies. The most commonly used antibodies in these RDTs reacted to either 2 bands (1 antigen) of histidine-rich protein (HRP-2) or aldolase and plasmodium lactate dehydrogenase (pLDH). HRP-2 is typically a marker for

TABLE 1

Commonly employed rapid diagnostic tests (RDTs) for the diagnosis of *Plasmodium falciparum*

	No. of trials	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)
All HRP-2 trials (vs microscopy)	75	95.0 (93.5–96.2)	95.2 (93.4–96.6)
All pLDH trials (vs microscopy)	19	93.2 (88.0–96.2)	98.5 (96.6–99.4)
Only trials directly comparing HRP-2 and pLDH	HRP-2 (vs microscopy)	9	95.6 (90.0–98.1)
	pLDH (vs microscopy)	9	94.8 (84.1–98.2)

HRP-2=histidine-rich protein marker for *P falciparum*; pLDH=plasmodium lactate dehydrogenase marker for multiple *Plasmodium* species.

TABLE 2

Comparison of rapid diagnostic tests (RDTs) to light microscopy in the diagnosis of *Plasmodium falciparum* in children ages 2 months to 5 years

Antigens	Sensitivity (95% CI)	Specificity (95% CI)	LR+	LR–	
HRP-2	1	94 (92–95)	62 (59–66)	2.47	0.13
pLDH	1	88 (86–90)	80 (77–83)	4.4	0.15
Combination	2	88 (85–89)	82 (78–84)	4.89	0.15

HRP-2=histidine-rich protein marker for *P falciparum*; pLDH=plasmodium lactate dehydrogenase marker for multiple *Plasmodium* species; LR+=positive likelihood ratio; LR–=negative likelihood ratio.

P falciparum, detectable up to 28 days after antimalarial therapy. pLDH can be a marker for many infections (*P falciparum*, *P vivax*, *P ovale*, and *P gambiae*). HRP-2 antibody-based tests and pLDH antibody-based tests were compared with microscopy. HRP-2 and pLDH were also compared directly in some of the studies (see **TABLE 1**).

According to the Cochrane authors, *P falciparum* either in isolated or mixed infection is most likely in sub-Saharan Africa and lowlands of Papua New Guinea, and single-antigen HRP-2 RDTs for *P falciparum* are accurate and clinically relevant. In other areas (Asia, Americas, Ethiopian highlands), due to a high likelihood of isolated infections with either *P falciparum* or *P vivax*, combined antigen HRP-2 and pLDH RDTs, which can diagnose both species, are recommended.¹

A 2014 diagnostic cohort study of Ugandan children (age range 2 months to 5 years) presenting with acute febrile symptoms (N=1,648) compared a 2-antigen HRP-2/pLDH combination RDT with a standard single-antigen HRP-2 RDT for diagnosis of *P falciparum* using light microscopy as the reference standard.²

TABLE 2 illustrates an increased specificity with the dual-antigen test compared with the HRP-2; however, the

sensitivity and positive and negative likelihood ratio of dual-antigen tests largely reflect those of the pLDH test alone. This leaves the clinical utility of a dual-antigen test unclear.

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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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Are antihistamines an effective treatment for drug-induced bone pain?

EVIDENCE-BASED ANSWER

Loratadine, given concurrently with granulocyte-colony stimulating factor (G-CSF), does not prevent bone pain more than placebo (SOR: **B**, single RCT). Hydroxyzine or astemizole (no longer available) given before or concurrently with G-CSF, are associated with less growth factor-induced bone pain (SOR: **C**, prospective cohort study and case reports).

A 2016 randomized, multicenter study assessed the prophylactic effect of loratadine on G-CSF-induced bone pain.¹ In the first stage, 213 patients scheduled to receive a first-time dose of pegfilgrastim 6 mg subcutaneously along with chemotherapy were identified. Significant bone pain, defined as a 2-point increase in leg/back pain on the Worst Pain Scale (range 0–10) during the 7 days after pegfilgrastim administration and a score of at least 5 on day 8, occurred in 30.5% (65/213) of patients.

In the second stage, 46 patients with significant pain in stage one were randomized to receive loratadine 10 mg (n=22) or placebo (n=24) once daily for 7 days, beginning on day 1 of pegfilgrastim therapy. Type of malignancy and taxane use (known to cause more bone pain) was similar across study arms. At baseline, 4 patients (18.2%) in the loratadine arm and 2 patients (8.3%) in placebo arm reported using NSAIDs, and 5 (22.7%) and 6 (25%) patients reported non-NSAID analgesic use, respectively. By day 8, 6 additional patients in the loratadine arm reported using NSAIDs and 4 additional patients reported using non-NSAID analgesics; in the placebo group, 2 additional patients used NSAIDs and 2 used non-NSAID analgesics. No difference was noted in the rate of significant pain improvement (62.5% in the placebo group vs 77.3% in the loratadine group; $P=.35$).¹

A 2005 prospective cohort study examined the therapeutic effect of hydroxyzine for relief of G-CSF-induced bone pain.² Forty patients who received G-CSF were followed for 2 rounds of treatment. In the first round, patients received NSAIDs or hydroxyzine 50 mg twice daily after G-CSF administration. No information was provided regarding randomization or type of NSAID.

In the 4 patients who experienced bone pain, NSAIDs were not effective, although hydroxyzine was effective (no statistical analysis reported). With the next round of G-CSF, hydroxyzine was administered preventively to all patients, and none experienced pain.²

A 2014 case report described a 67-year-old patient with stage IV ovarian cancer and severe debilitating bone pain (pain score 10/10) secondary to G-CSF administered 24 hours after the third round of chemotherapy and all subsequent cycles.³ She failed treatment with naproxen 400 mg, 3 times daily, and experienced minimal relief with both oxycodone 5 to 10 mg and hydromorphone 1 to 2 mg every 4 to 6 hours as needed.

During subsequent chemotherapy cycles, naproxen and opioids were discontinued and she was treated with loratadine 10 mg daily for 7 days beginning the day before chemotherapy. Prevention of pain was achieved. The patient was monitored over the course of the next 8 doses of G-CSF and maintained long-term pain relief with prophylactic loratadine alone, without the need for opioids or breakthrough pain medication.³

In a 1995 case report, a 59-year-old woman with bilateral breast cancer had G-CSF-induced bone pain that did not respond to treatment with acetaminophen.⁴ Her chemotherapy regimen included monthly Taxol infusions followed by G-CSF for 10 days. She subsequently received astemizole (no longer marketed in United States) 30 mg on day 1, 20 mg on day 2, and 10 mg on days 3 to 10 along with the G-CSF and did not experience pain throughout the chemotherapeutic cycle.

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Is eye movement desensitization and reprocessing an effective treatment modality for panic disorder?

EVIDENCE-BASED ANSWER

Eye movement desensitization and reprocessing (EMDR) may improve some measures of symptoms associated with panic disorder, but has inconsistent effects on frequency of panic attacks (SOR: **C**, based on 2 small RCTs). EMDR may produce long-term results similar to those of cognitive behavioral therapy (CBT) and has slightly faster improvement in symptoms (SOR: **C**, single small RCT).

EMDR is a method of psychotherapy by which a client focuses on emotionally disturbing memories while simultaneously focusing on therapist-directed lateral eye movements. The technique involves an 8-step protocol that guides the client to attend to past hurts, current stressors, and positive future actions.

A single-blinded, RCT from 2000 compared the efficacy of EMDR versus waiting list and a credible attention-placebo control in a total of 46 outpatients.¹ The EMDR protocol included six 90-minute sessions held over an average of 4 weeks. The credible attention-placebo control involved contact with a therapist for the same amount of time as the EMDR group using 30 to 45 minutes of progressive muscle relaxation training and 45 to 60 minutes of association therapy. Patients were aged 18 to 65 years and met DSM-IV criteria for panic disorder of at least 1 year's duration with at least moderate agoraphobia for the prior 6 months.

Patients completed a series of 10 validated, self-reported questionnaires on symptoms of fear, panic-related somatic symptoms, cognitions related to panic (feared consequences, anticipation, and appraisal of coping resources), agoraphobic avoidance, depressive symptoms, general anxiety, and global functioning, along with a structured symptom severity interview. Data were collected 1 week before, 1 week after, and 5 to 6 weeks after the intervention, combined into a single outcome and reported as effect size.¹

EMDR had a moderate effect on panic/agoraphobia severity (effect size 0.71) and was superior to waiting list (effect size 0.01; $P<.05$). No difference was noted in panic attack frequency. No significant differences were noted in any outcome variables comparing EMDR and attention-placebo control.¹

An Italian RCT from 2012 compared EMDR and CBT for the treatment of panic disorder.² A total of 20 patients (12 women, 8 men; age range 20–48 years) with panic disorder (with or without agoraphobia) according to DSM-IV guidelines were divided into EMDR and CBT treatment groups and underwent 24 weeks of once-per-week therapy. The patients were evaluated with 5 inventories at the beginning of treatment, after 12 and 24 weeks, and at 3-month and 1-year follow-up intervals. The inventories measured the number and type of panic attacks, disturbing phobias and fears, degree of work and interpersonal impairment, and anxiety/panic symptom severity.

EMDR and CBT groups showed similar trends in symptom improvement, indicating that both treatment modalities could be effective treatments for panic disorder. Although EMDR produced faster symptomatic improvement and greater resolution of anticipatory anxiety, statistical analysis of these differences was not reported.²

Another RCT from 1997 compared EMDR (6 sessions) versus EFER (eye fixation exposure and reprocessing) versus a waiting list in 43 patients meeting DSM-III-R diagnosis of panic disorder.³ Outcomes were measured 1 week prior to treatment, 1 week after treatment, and 3 months after treatment using validated questionnaires. Self-monitoring records were also completed nightly starting 2 weeks pretreatment and ending 2 weeks posttreatment. Panic frequency was included as the final outcome variable.

At the 1-week posttreatment analysis, EMDR showed significantly greater improvement in all measures compared with wait-list. Specifically, on 11-point scales, mean scores for highest anxiety decreased by 1.1 points with EMDR versus 0.49 points for wait list; average anxiety scores decreased by 2.1 points with EMDR versus 0.24 points for wait list; and fear of panic scores decreased by 0.94 points with EMDR versus 0.21 points for wait list ($P<.05$ for all comparisons). Mean number of panic attacks over a 2-week period decreased by 2.4 for those in the EMDR group versus 1.7 for those in the wait-list group ($P=.001$). Although

there were some initial differences favoring EMDR over EFER, at 3-month follow-up, no significant differences were noted between EMDR and EFER on any measures.³

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Is acupuncture safe and effective for rheumatoid arthritis?

EVIDENCE-BASED ANSWER

Acupuncture does not reduce pain in patients with rheumatoid arthritis (RA) compared with sham acupuncture (SOR: **B**, systematic reviews of limited quality RCTs). In contrast, electroacupuncture may be more effective than sham acupuncture (SOR: **C**, small, limited quality RCT). Acupuncture with moxibustion may be equal to NSAIDs in reducing pain (SOR: **B**, systematic review of limited quality RCTs). Evidence is insufficient to assess the safety of acupuncture therapy (SOR: **C**, systematic review of RCTs and case reports).

A 2008 systematic review identified 8 RCTs (N=550) evaluating pain reduction with acupuncture in patients of any age with RA.¹

Meta-analysis of 3 acupuncture versus penetrating sham acupuncture studies (n=88) showed no improvement in pain measured on a 4-point Likert or visual analog scales (VAS) (weighted mean difference [WMD] -0.46; 95% CI, -1.7 to 0.77). Meta-analysis of 2 studies comparing acupuncture with moxibustion (traditional Chinese method using burning mugwort to stimulate acupuncture points) to NSAID therapy (n=105) showed no difference in pain reduction on a 10-cm VAS (WMD 1.53; 95% CI, -0.57 to 3.6). NSAIDs used were indomethacin 25 or 50 mg 3 times daily or diclofenac (dose not reported) twice daily.¹

Authors concluded that current evidence was insufficient to provide support for or against the treatment of RA pain with acupuncture. They acknowledge potential publication bias against negative outcomes, raising concern over treatment safety.¹

A 2005 Cochrane review of 2 RCTs (N=84) assessed the effects of acupuncture on pain associated with RA in patients aged 18 and older.² Both studies were included in the systematic review above and there was insufficient data for meta-analysis, but this review reported the results of the trials.

One study used the comparator of nonpenetrating sham acupuncture versus traditional acupuncture and showed no improvement in pain measured on a VAS (range not reported) 6 weeks after a series of 5 once-weekly, 4-minute-long treatments of a single bilateral acupuncture point compared with nonpenetrating sham treatment (n=64; WMD -7.00; 95% CI, -14.40 to 0.40). The other study used electroacupuncture instead of traditional acupuncture. A single electroacupuncture treatment, compared with penetrating sham acupuncture, reduced knee pain measured on a nonvalidated pain reduction scale (0 indicating no residual pain, 4 indicating no pain reduction) at 24 hours (n=20; WMD -2.0; 95% CI, -3.6 to -0.40) and again 4 months after treatment (WMD -0.2; 95% CI, -0.36 to -0.04). The review authors were unable to offer support for or against the use of acupuncture in patients with RA.²

A 2011 systematic review addressed the safety of acupuncture.³ Of 266 systematic reviews or meta-analyses found, 57 were included and 95 individual reports of infection, organ trauma, or other complications that required intervention were found within. Adverse events resulted in death in 5 cases of pneumothorax. No discussion of the number of cases reviewed nor the sample size from which these reports could have resulted was provided. Authors used these data to caution against drawing positive conclusions of acupuncture effectiveness and to advocate further study. **EBP**

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