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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.

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EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

STATEMENT OF PURPOSE

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

EDITORIAL POLICY

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

DISCLOSURE

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Steps to heart health

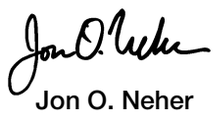
I was initially puzzled by the 10,000 steps craze that swept through the office several years ago. My trendier colleagues were suddenly sporting colorful fitness trackers and letting all of us know how many thousands of steps they had completed. Eventually, even my hospital administration got on the bandwagon and started awarding health insurance premium offsets for downloading fitness tracker data to a third party "lifestyle" vendor.

It turns out the 10,000-step target was something of a mirage, created by a bit of slick marketing. An early pedometer in Japan was called the "10,000 step meter," a name chosen because the Japanese character for 10,000 (万) was thought to look something like a person walking.[1] The 10,000-step goal was thereafter associated with fitness tracking, but the goal did not have any science behind it.

Fortunately, someone finally did the science.[2] Researchers in the Netherlands decided to review all studies that compared measured step counts with cardiovascular health outcomes. They identified 12 prospective cohort trials with 111,309 adult step-counters without known cardiovascular disease at baseline. This group was 60% women, with a mean age of 62 years old and a mean BMI of 27 kg/m^2. Most studies had a low risk of bias. The mean follow-up time was 78 months and, for statistical purposes, 2,000 steps a day was chosen as the normal comparator.

It turns out, small improvements in all-cause mortality were noted with as few as 2,517 steps a day (adjusted hazard ratio [aHR] 0.92; 95% CI, 0.84–0.99). Researchers found that the optimum number of steps was 8,763 for all-cause mortality reduction (aHR 0.40; 95% CI, 0.38–0.43) and 7,126 for incident cardiovascular disease reduction (aHR 0.49; 95% CI, 0.45–0.55). People who walked faster had additional risk reduction. People who walked farther did not (although the sample size was smaller).

This means optimum heart health can come with walking just four to five miles a day—a number that doesn't need exponents, I can count on one hand, and allows me to skip the fitness tracker whenever there are milage markers.



Jon O. Neher

DOI 10.1097/EBP.0000000000002137

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Does it matter, I forgot to take my vitamins?

Yeung LK, Alschuler DM, Wall M, et al. Multivitamin Supplementation Improves Memory in Older Adults: A Randomized Clinical Trial. *Am J Clin Nutr*. 2023;118(1):273-282. doi:10.1016/j.ajcnut.2023.05.011

DOI 10.1097/EBP.0000000000002096

The Cocoa Supplement and Multivitamin Outcomes Study-Web (COSMOS-Web) trial was a randomized, double blind, placebo-controlled trial to investigate the effect of dietary flavanol supplementation on memory in older adults. Participants were 93.3% White, and 94.5% had completed at least some college-level education. Pill compliance was not accounted for in the statistical analysis. This study was conducted within the COSMOS Study (n=21,442) evaluating effects of cocoa and multivitamin use on cardiovascular and cancer outcomes. Because the COSMOS-Web trial was conducted inside the larger study evaluating multivitamin use, the investigators of this trial looked at the effect of multivitamin (Centrum Silver) use on memory. The COSMOS-Web multivitamin trial included 3,562 adults (1,758 multivitamin and 1,804 placebo) 60 years old and older (men 60 years old and older and women 65 years old and older) who were without history myocardial infarction, stroke, invasive cancer, and other serious medical illness. Patients stopped taking other dietary supplements (multivitamins, calcium [≥1,500 mg/d], vitamin D [≥2000 IU/d], and cocoa extract) and maintained at least 75% adherence during a two-month placebo run-in period by self-report. Patients were required to communicate in English and use a computer to perform study tests and report compliance. Patients were given either a multivitamin or a placebo. The primary outcome was performance on immediate recall using the ModRey test (MDRI) at one year. Secondary outcomes were results of the MDRI recall at two and three years—the ModRey retention (MDRR) (the ratio of delayed recall to immediate recall), performance on tests of novel object recognition (ModBent), and executive function (Flanker). The MDRI assessment was a web-based test where the patient was presented with 20 words, each for three seconds, and asked to recall as many words as possible immediately after being exposed to the last word in the list. The MDRR was a similar assessment; however, patients were asked to recall as many words as possible 15 minutes after being exposed to the last word in the list. Patients in the multivitamin arm (baseline 7.10 words and 7.81 words at 1 year) did better than patients in the placebo arm (baseline 7.21 words and 7.65 words at 1 year). This difference was statistically significant, but the actual difference (AD) of .27 words was very close to the calculated standard error (SE=.23, t-statistic t(5889) = 2.25, *P*=.025). There was also a statistically significant difference over the three years in the MDRI (AD=.21 words, SE=.15, t(5889) = 2.54, *P*=.011). An intention-to-treat analysis was performed. No other outcomes measures were statistically significant. Increased gastrointestinal bleeding was reported in the multivitamin group; however, no specificity of severity or frequency was reported.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching PUBMED with the terms [Multivitamin; memory; older adults] completed on September 13, 2023 to find additional literature to place this research into the context of current clinical practice.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	No

Bottom line: While multivitamin supplementation is a relatively inexpensive and accessible health intervention, it is unlikely multivitamin supplementation improves immediate recall memory despite the statistically significant results in this study.

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Not all about statins—bempedoic acid use for CVD protection in statin-intolerant patients

Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N Engl J Med*. 2023. doi: 10.1056/NEJMoa2215024

DOI 10.1097/EBP.0000000000002064

This double-blind, randomized, placebo-controlled trial investigated the effects of bempedoic acid on cardiovascular outcomes in statin-intolerant adults with cardiovascular disease or high risk of cardiovascular disease (N=13,970). Statin-intolerant patients are defined as those who were unable or unwilling to take statins because of patient-perceived unacceptable adverse effects. Patients were mostly White (91%) adults aged 18 to 89 years old, of which 70% had a previous cardiovascular event and 46% had diabetes. The patients were assigned to receive oral bempedoic acid 180 mg daily or placebo over 60 months (median follow-up 41 months). The baseline mean LDL cholesterol level in both groups was 139 mg/dL. The primary outcome was a composite of major adverse cardiovascular events (MACE), defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. Secondary outcomes included rates of myocardial infarctions, strokes, coronary revascularizations, death from cardiovascular causes, and death from any cause.

Patients in the bempedoic acid group demonstrated a 1.6% reduction in MACE composite as compared with placebo (hazard ratio [HR] 0.87; 95% CI, 0.79–0.96; *P*=.004; NNT=63). LDL cholesterol declined by 21% at six months from baseline with bempedoic acid. Compared with placebo, bempedoic acid use showed a 1.1% reduction in fatal or nonfatal myocardial infarction (HR 0.77; 95% CI, 0.66–0.91; *P*=.002; NNT=91) and a 1.4% reduction in coronary revascularization (HR 0.8; 95% CI, 0.72–0.92; *P*=.001; NNT=72). No statistically significant difference was noted in rates of stroke, death from cardiovascular causes, or death from any cause. Both gout and cholelithiasis events were higher with bempedoic acid than with placebo. Limitations of the study include patient-defined statin intolerance and no distinction between primary and secondary prevention patients.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching [UpToDate, DynaMed, and PubMed] with the terms [Bempdeoic acid] to find additional literature to place this research into the context of current clinical practice.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	No

Bottom line: Among statin-intolerant adults with cardiovascular disease or significant risk of cardiovascular disease, the use of bempedoic acid is associated with a decrease in a cardiovascular composite outcome and a reduction in myocardial infarction and coronary revascularization when compared with placebo; however, no difference was noted in the incidence of stroke, cardiovascular mortality, or all-cause mortality when compared with placebo. Bempedoic acid is an alternative for patients who cannot take the first-line treatment. Further research comparing bempedoic acid against alternative nonstatin therapies may further clarify its role in primary and secondary prevention for statin-intolerant patients.

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Getting the bang for your buck with denosumab—diabetes risk reduction while treating osteoporosis

Lyu H, Zhao SS, Zhang L, et al. Denosumab and incidence of type 2 diabetes among adults with osteoporosis: population based cohort study. *BMJ*. 2023;381:e073435. doi: 10.1136/bmj-2022-073435

DOI 10.1097/EBP.0000000000002095

In this large retrospective cohort study, adult patients being treated for osteoporosis with oral bisphosphonates or denosumab were observed and monitored for the onset of type II diabetes. Researchers used a large UK primary care database to find patients 45 years old and older, who had initiated denosumab 60 mg or received an oral bisphosphonate (alendronate 10 mg or 70 mg, ibandronate 150 mg, risendronate 35 mg) between July 1, 2010, and December 31, 2021. A propensity score was used to best match users of denosumab with similar users of bisphosphonates, using a 1:5 match ratio, for comparison. Factors taken into consideration for the propensity match included age, sex, smoking status, comorbidities, BMI, medications, socioeconomic status, duration of treatment, and general health status. Patients using denosumab were then divided into two groups; incident new users of denosumab and those who had been on a bisphosphonate and then switched to denosumab, called "prevalent users." There were 4,350 potentially eligible patients started on denosumab and 207,481 potentially eligible individuals initiated on an oral bisphosphonate. Researchers excluded patients enrolled less than 365 days by end of trial, patients with Paget disease of the bone, and any patient who had previously used antidiabetic medication before the index date. A total of 4,301 new denosumab users were matched on propensity scores with 21,038 users of oral bisphosphonates (1:5). In the propensity-matched populations, patients were highly comparable with a standardized difference of <0.1 for baseline characteristics. Patients were assessed from start of first prescription until whatever occurred first: diagnosis of diabetes mellitus; stoppage of the drug; death; departure from clinic; five-year follow up; or December 31, 2021, marking the end of the study. The primary outcome was the incidence of type II diabetes based on numerous well-accepted diagnostic criteria.

The mean time of follow-up across the study was 2.2 years. The incidence of type II diabetes per 1,000 person-years was 5.7 (95% CI, 4.3–7.3) in the denosumab group and 8.3 (95% CI, 7.4–9.2) in the oral bisphosphonate group (hazard ratio [HR], 0.68; 95% CI, 0.52–0.89). This resulted in a number needed to treat (NNT) of 388 to prevent one additional case of diabetes per 1,000 person years. Additional analysis also demonstrated a decreased risk of developing diabetes in the denosumab group compared with the oral bisphosphonates group for those diagnosed with prediabetes (11.8 vs 22.1 per 1,000 person-years; HR, 0.54; 95% CI 0.35–0.82; NNT=99). Two clear limitations of the study include the short mean follow-up duration (2 years) and the low number of outcome events in the denosumab group— facts that prompted the study authors to state that their results should be "hypothesis-generating" for future randomized controlled trials rather than being taken as unequivocal evidence.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching UpToDate and Dynamedex with the terms Denosumab AND Osteoporosis, diabetes AND Denosumab to find additional literature to place this research into the context of current clinical practice.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	No

Bottom line: While the findings of this study are intriguing and valid, when one considers the overall cost of denosumab and the relatively small benefit in preventing the development of type 2 diabetes (NNT=388 to prevent 1 new case of diabetes per 1,000 person-years), the overall utility proves quite limited. In those already diagnosed with prediabetes, the consideration may increase ever so slightly as the NNT improves to 99.

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The authors declare no conflict of interest.

At last! Experimental data on spironolactone for acne

Santer M, Lawrence M, Renz S, et al. Effectiveness of spironolactone for women with acne vulgaris (SAFA) in England and Wales: pragmatic, multicentre, phase 3, double blind, randomised controlled trial. *BMJ*. 2023;381:e074349. doi:10.1136/bmj-2022-074349

DOI 10.1097/EBP.0000000000002099

A multicenter, randomized, placebo-controlled trial from the United Kingdom evaluated spironolactone for the treatment of acne in adult women for at least six months with an initial severity of at least two on the five-point Investigator's Global Assessment scale (IGA; 0=clear, 4=severe). Patients were excluded if they had ever taken spironolactone or had recently taken isotretinoin or oral antibiotics. Hormonal contraception and previous topical treatments were allowed. Investigators included 410 women with an average age of 29 years old. After randomization, 201 patients received spironolactone 50 mg daily for six weeks, then 100 mg daily for a total of 24 weeks, and 209 patients received matching placebo. The primary outcome was the mean difference between groups at 12 weeks in the Acne-Specific Quality of Life (Acne-QoL) symptom subscale score (range 0–30 with higher scores indicating improved symptom-related quality of life), adjusted for baseline score, use of topical and hormonal treatments, age, and PCOS diagnosis. Baseline scores were 13.2 in the spironolactone group and 12.9 in the placebo group. There were numerous secondary outcomes including the Acne-QoL symptom subscale at 24 weeks, patient-assessed overall improvement on a six-point Likert scale, success on the IGA (score of 0 or 1 at 12 weeks), and success on the Participant Global Assessment (PGA, same scale as the IGA). At 12 weeks, the mean Acne-QoL symptom subscale score in the spironolactone group was 19.2 versus 17.8 in the placebo group (adjusted mean difference 1.3; 95% CI, 0.07–2.5) representing less than a 5% difference on the 30-point scale. At 24 weeks, this increased to an adjusted mean difference of 3.5 (95% CI, 2.2–4.8), but this was still only a 12% difference on the 30-point scale. Other secondary outcomes had mixed results, which were generally better at 24 weeks than at 12 weeks. No difference was observed in self-assessed overall improvement ($\geq$3 on the 6-point Likert scale) at 12 weeks, but at 24 weeks, 82% of the spironolactone group reached this point versus 63% of the placebo group (adjusted odds ratio [aOR] 2.7; 95% CI, 1.5–4.9). Success on the IGA at 12 weeks was reached by 19% in the spironolactone group versus 6% in the placebo group (aOR 5.2; 95% CI, 2.2–12). No difference was observed in success on the PGA at 12 weeks, but at 24 weeks, 32% in the spironolactone group and 11% in the placebo group self-rated success (aOR 3.8; 95% CI, 2.0–7.3).

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching DynaMed, UpToDate, Cochrane Library, and Pub Med with the terms "acne" and "acne-specific quality of life questionnaire" to find additional literature to place this research into the context of current clinical practice.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	No

Bottom line: This RCT adds to previous observational studies and shows spironolactone leads to statistically significant improvements in symptom-related acne quality of life. However, this improvement is likely not clinically significant at 12 weeks and of borderline clinical significance at 24 weeks. Additional outcomes show inconsistent results at 12 weeks that generally became more consistently positive by 24 weeks.

Patients may be discouraged with having to wait 24 weeks to see clinically meaningful results. Future trials should consider a more aggressive dose titration schedule to see whether meaningful results can be achieved earlier. As with some other acne treatments, spironolactone is contraindicated in patients who are pregnant or attempting to conceive.

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The authors declare no conflict of interest.

Does stopping statin therapy used for primary prevention in older persons increase the risk of fatal or nonfatal cardiovascular outcomes?

EVIDENCE-BASED ANSWER

Older adults who discontinue primary prevention statin therapy may experience an excess of one major adverse cardiovascular event for every 112 persons (SOR: **B**, large cohort study) and a 30% increase in hospital admission for cardiovascular events (SOR: **B**, large cohort study). Statin discontinuation in older adults receiving polypharmacy for other conditions including antidiabetes, antiplatelet and antihypertensive therapies is similarly associated with an increase in fatal and nonfatal cardiovascular outcomes (SOR: **B**, large cohort study).

DOI 10.1097/EBP.0000000000002030

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 Danish cohort study identified 27,463 patients 75 years old or older taking statin medications for primary prevention and examined the association between statin discontinuation and major adverse cardiovascular events (MACEs) defined as myocardial infarction, ischemic stroke, transient ischemic attack, coronary revascularization procedure, or death from myocardial infarction or ischemic stroke.[1] Patient and prescription data were obtained from the Danish Health Data Authority. The cohort population was 66% female with a median age of 79 years old and included 34% with hypertension, 35% with diabetes, and 10% with atrial fibrillation. Patients had received at least five years of statin therapy (96.2% were low or moderate intensity). Statin discontinuation was defined as an unfilled statin prescription for at least 180 days, whereas statin continuation was defined as no gaps in therapy >180 days. The primary outcome measure was MACE during follow-up with a median duration of 5.5 years. The rate of occurrence of MACE was higher in the discontinuation group than in the continuation group (hazard ratio [HR] 1.3; 95% CI, 1.2–1.5), which corresponded to an excess of one MACE for every 112 persons who discontinued statins per year. This study was limited by lack of data regarding reasons for statin discontinuation and lack of control for development of additional comorbidities that may have influenced statin discontinuation or risk of acute cardiovascular outcomes.

A 2019 retrospective cohort study (n=120,173) using a French national health insurance claims database examined the impact of discontinuation of statins on cardiovascular outcomes.[2] Patients were predominantly females (59.2%) at least 75 years old who were adherent to statins for at least two years for primary prevention. Patients with preexisting coronary disease or inconsistent prescriptions of statins were excluded. Most of the patients (79%) were also taking antihypertensive medications and 24.4% had diabetes. The study group discontinued statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin at variable intensity doses) for at least three consecutive months, whereas the comparison group continued statin use. The primary outcome was hospital admission for cardiovascular events over a maximum of four years, with an average follow-up of 2.4 years. Follow-up was stopped if a patient experienced the primary outcome, resumed statin therapy, or died. Of the total cohort, 14.3% discontinued statins and 4.5% were admitted for a cardiovascular event. The adjusted hazard ratios for statin discontinuation were significant for hospital admission for any cardiovascular event (HR 1.3; 95% CI, 1.2–1.5), coronary event (HR 1.5, 95% CI, 1.2–1.8), and cerebrovascular event (HR 1.3; 95% CI, 1.1–1.5). This population cohort study was limited by lack of generalizability, challenges of correlating pharmacy fill data with actual use, lack of data on reasons for statin discontinuation, and lack of data on detailed medical and socioeconomic data from patients.

A 2021 retrospective cohort study examined the clinical implications of discontinuing statin therapy while continuing other medications in 29,047 patients 65 years old or older who were receiving polypharmacy (defined as taking a statin, blood pressure lowering, antidiabetic, and antiplatelet agent).[3] Researchers retrieved patient

and prescription data from healthcare utilization databases in Lombardy, Italy. Patients had a mean age of 76.5 years old and were predominantly male (63%); 19.7% had ischemic heart disease, 7.9% had cerebrovascular disease, and 7.9% had heart failure. The study defined statin discontinuation as a gap of greater than 90 days between prescription renewals. Patients who discontinued statins while continuing other medications (n=4,203) were compared with patients who continued statins using a propensity score matching scheme to help control for covariants such as age, sex, comorbidities, and medication adherence. The primary outcomes were hospital admissions for cardiovascular events, all-cause mortality, and emergency department visits. Patients who discontinued statins had an increased risk of hospital admissions for heart failure (HR 1.2; 95% CI, 1.1–1.4), any cardiovascular outcome (HR 1.1; 95% CI, 1.0–1.3), all-cause mortality (HR 1.2; 95% CI, 1.0–1.3), and emergency department visits (HR 1.1; 95% CI, 1.0–1.2) compared with patients who continued statin therapy. In subgroup analyses, patients who discontinued statins after taking them for primary prevention had similar risks as those taking them for secondary prevention in hospital admissions for cardiovascular events, all-cause mortality, and emergency department visits (*P* value not significant for all comparisons; number of patients in each group not provided). The study was limited by possible missing data due to care received that was not captured by the healthcare database. EBP

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Evaluating treatment of acute migraine with zavegepant 10 mg nasal spray

Safety, tolerability, and efficacy of zavegepant 10 mg nasal spray for the acute treatment of migraine in the United States: a phase 3, double-blind, randomized, placebo-controlled multicenter trial

Lipton RB, Croop R, Stock DA, et al. Safety, tolerability, and efficacy of zavegepant 10 mg nasal spray for the acute treatment of migraine in the United States: a phase 3, double-blind, randomized, placebo-controlled multicenter trial. *Lancet Neurol*. 2023; 22(3):209-217. doi: 10.1016/S1474-4422(22)00517-8 DOI 10.1097/EBP.0000000000002013

KEY TAKEAWAY: Zavegepant nasal spray was efficacious in reducing pain and bothersome symptoms in acute treatment of migraines when compared with placebo.

STUDY DESIGN: Phase 3, randomized, double-blind, placebo-controlled multicenter trial

LEVEL OF EVIDENCE: STEP 2

BACKGROUND: Current migraine medications (most commonly triptans) have limited efficacy and significant contraindications for certain populations. Oral calcitonin gene-related peptide (CGRP) receptor antagonists are a newer class of migraine medications that have been shown to be increasingly safe and effective for treating acute migraine. There is yet to be a nonoral formulation of a CGRP antagonist.

PATIENTS: Adults with history of migraine
INTERVENTION: Zavegepant 10 mg nasal spray
CONTROL: Placebo spray
OUTCOME: Primary outcomes: two coprimary outcomes—pain freedom and freedom from most bothersome migraine symptoms at two hrs after first dose
SECONDARY OUTCOMES: Multiple, including patient's need for rescue medication, pain relapses, and ability to function normally

METHODS BRIEF DESCRIPTION:

- Adults with a history of 2 to 8 moderate/severe migraines a month for at least one year; 1,405 patients in total were eligible and participated in the study.
- An independent research organization managed the randomization, and all study personnel were masked to treatment assignments.
- Patients were blinded and randomized to one of the following treatments:
  - Zavegepant 10 mg nasal spray
  - Matching placebo
- Patients self-administered a single spray from the device when they experienced a moderate-severe migraine with bothersome symptoms.
- Patients were given an electronic device to record onset of migraine, associated symptoms, pain scale, and level of disability at certain periods during migraine.
- Patients had a follow-up visit within seven days of treated attack where data in the electronic recording device were reviewed, tolerability and safety of medication assessed, and compliance determined.
- Pain intensity was measured on a four-point scale (0=none, 1=mild, 2=moderate, 3=severe) with pain freedom being a score of 0.
- Freedom from most bothersome symptoms (chosen from photophobia, phonophobia, or nausea) was characterized as 0=absent and 1=present.

INTERVENTION (# IN THE GROUP): 703 randomized, 623 completed study

COMPARISON (# IN THE GROUP): 702 randomized, 646 completed study

FOLLOW UP PERIOD: Within seven days of treatment

RESULTS:

Primary outcome:

- Zavegepant treated patients were more likely to have the following compared with placebo:
  - Freedom from pain at two hours (absolute risk reduction 8.8%; 95% CI, 4.5–13; NNT=12)
  - Freedom from the most bothersome symptom at two hours (absolute risk reduction 8.7%; 95% CI, 3.4–14; NNT=12)

Secondary outcomes:

- Zavegepant was statistically better than placebo for most secondary outcomes.

- Three secondary outcomes were not statistically significant including ability to function normally within 15 minutes, no pain relapse at 2 to 48 hours, and freedom from nausea at two hours.

LIMITATIONS:

- Because the study design was based on a single migraine attack, it does not provide long-term data on safety and consistency.
- The results of the study could not be compared with other approved migraine medications because there was no active comparator.
- Trial was conducted at academic centers, headache clinics, and independent research facilities which can limit its applicability to a primary care patient. EBP

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The author declares no conflicts of interest.

Does tai chi improve fibromyalgia symptoms more than aerobic exercise?

EVIDENCE-BASED ANSWER

Tai chi practiced 1 to 2 hours a week for 24 weeks may be superior to aerobic exercise for improving fibromyalgia symptoms such as pain, fatigue, morning tiredness, depression, and anxiety and may also increase physical function, job difficulty, and overall well-being (SOR: **B,** single randomized controlled trial). Experts recommend offering physical exercise or tai chi for treating patients with fibromyalgia symptoms (SOR: **C,** consensus guidelines).

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A 2018 single-blind randomized controlled trial compared the effectiveness of tai chi and aerobic exercise in 226 patients with fibromyalgia at an urban tertiary care academic hospital in the U.S.[1] Patients had a mean age of 52 years (92% were women and 61% were White) and had fibromyalgia diagnosed by the American College of Rheumatology criteria, with body pain for an average of nine years. None had participated in tai chi or other modes of alternative medicine in the six months before trial enrollment. Medication use included 85% taking NSAIDs, 58.4% taking antidepressants, and 30.1% taking anticonvulsants. The intervention consisted of supervised 1-hour sessions of classical Yang style tai chi, and the researchers randomly assigned 151 patients to one of four groups: tai chi once or twice weekly, each for 12 or 24 weeks. A comparator group (n=75) participated in supervised aerobic exercise sessions twice weekly for 24 weeks; each session lasted approximately 1 hour. Patients were followed for 52 weeks, and the primary outcome was a change in the revised fibromyalgia impact questionnaire (FIQR) score, assessed at baseline and at the end of 24 weeks. The FIQR (range 0–100, with lower scores indicating improvement) measures patient-rated fibromyalgia symptom and severity. The investigators considered a FIQR score change of 8.1 to be the minimum clinically important difference. Average FIQR scores from baseline to 24 weeks improved in all five groups; the difference in improvement was greater in the combined tai chi groups compared with the aerobic exercise group, but it was not clinically important (mean difference [MD] –5.5 points; 95% CI, –10.4 to –0.6). However, for patients participating in twice weekly sessions for 24 weeks, tai chi provided a clinically important improvement in FIQR scores compared with aerobic exercise (MD –16.2 points, 95% CI, –23.6 to –8.7). The study found no significant differences in FIQR scores between patients participating in tai chi once versus twice weekly (MD 4.5 points, 95% CI, –2.5 to 11.4 at 24 weeks). All groups reported slightly less improvement in FIQR scores at 52 weeks compared with 24 weeks, noting an increase between 1 and 3 points on the 100-point scale. No serious adverse events were related to either of the interventions. The trial was limited by a higher attendance rate in the tai chi group (62%) compared with the aerobic exercise group (40%) and a 30% dropout rate during the 52-week study.

A 2017 research evidence and consensus-based guideline from the European League Against Rheumatism on the management of fibromyalgia emphasized prompt diagnosis, patient education, movement, and mindfulness-based activities before pharmaceutical intervention.[2] Exercise received a strong recommendation because of its perceived efficacy in treating pain and improving well-being without having high costs and adverse effects. Meditative movements (such as qigong, yoga, tai chi, or a combination of these therapies) were given a weak recommendation (based on systematic reviews and expert opinion with 71% agreement).

A 2014 evidence and consensus-based clinical practice guideline from the Department of Veteran Affairs on the management of chronic multisymptom illness (CMI) recommended offering yoga or tai chi for patients with CMI and fibromyalgia symptoms (weak recommendation, based on a systematic review of very low-quality evidence).[3] The guideline made similar recommendations to offer a program of physical exercise for patients with CMI and symptoms consistent with fibromyalgia

(weak recommendation, based on a systematic review of very low-quality evidence). EBP

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In adults with NVAF, which intervention best balances the prevention of thromboembolic events: stroke and systemic embolism with safety from bleeding complications?

EVIDENCE-BASED ANSWER

Compared with novel oral anticoagulants (NOACs) and vitamin K antagonist (VKA), left atrial appendage closure (LAAC) devices have significantly lower risk for major and nonprocedural bleeding and similar risk of all strokes, ischemic stroke, and systemic embolism (SOR: **A**, meta-analysis of randomized controlled trials [RCTs] and observational studies). Use of NOACs results in lower rates of all-cause mortality compared with a VKA, with no significant difference in safety between the two (SOR: **A**, network meta-analysis of RCTs).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 meta-analysis of five studies (N=4,778), consisting of three randomized controlled trials (RCTs) and two observational retrospective studies, compared the efficacy and safety of left atrial appendage closure (LAAC) devices versus medical therapy such as vitamin K antagonist (VKA) or novel oral anticoagulants (NOACs) in patients with nonvalvular atrial fibrillation (NVAF).[1] Patients were 61% to 75% male with a mean age of 73 years old, and followed for a median-weighted period of 2.6 years. The intervention group received different anti-embolic medications with no dosage information provided and different types of LAAC devices. The control group included placebo or no treatment. Studies with similar CHADS2-VASc and HAS-BLED scores were included, but no specific scores were reported. The primary safety outcomes included all-cause mortality, cardiovascular death, hemorrhagic stroke, major bleeding, nonprocedural major bleeding, all strokes, ischemic stroke, and systemic embolism. The primary efficacy outcomes included all stroke and systemic embolism. Compared with medical therapy, LAAC devices significantly reduced the risk of all-cause

mortality (3 studies, N=4,369; odds ratio [OR] 0.6; 95% CI, 0.46–0.77; I^2=62%), cardiovascular mortality (5 studies, N=4,778; OR 0.57; 95% CI, 0.46–0.70; I^2=0%), hemorrhagic stroke (3 studies, N=2,114; OR 0.19; 95% CI, 0.07–0.50; I^2=0%), major bleeding (4 studies, N=4,770; OR 0.61; 95% CI, 0.43–0.88; I^2=62%), and nonprocedural bleeding (2 studies, N=1,516; OR 0.46; 95% CI, 0.32–0.65; I^2=0%). No significant difference was noted in all strokes, systemic embolism, or ischemic stroke between LAAC and medical therapy. This study was limited that different types of LAAC devices were used across the studies included.

A 2016 network meta-analysis of 21 RCTs (N=96,017) compared the safety and efficacy with use of aspirin, VKA, NOACs (including apixaban, dabigatran, edoxaban, and rivaroxaban), and LAAC device (Watchman) among NVAF patients.[2] Patients were 65% male with a mean age range of 71.7 to 75.1 years old, and median follow-up period was 1.7 years. Trials were excluded if they had less than 200 patients, a prosthetic valve, mitral stenosis, high probability of bias, and less than six months of follow-up. The intervention group received aspirin, VKA, NOACs, or LAAC device. The control group had no treatment or placebo. The primary efficacy outcome was any stroke and systemic embolism, and secondary efficacy was all-cause mortality. The primary safety outcome was a combination of major extracranial bleeding and intracranial bleeding. Compared with placebo/control, use of aspirin (2 RCTs, N=1,539; OR 0.75; 95% CI, 0.60–0.95) and VKA (3 RCTs, N=600; OR 0.38; 95% CI, 0.29–0.49) significantly reduced any stroke and systemic embolism. Compared with placebo or control, use of individual NOACs—apixaban (OR 0.31; 95% CI, 0.22–0.45), dabigatran (OR 0.29; 95% CI, 0.20–0.43), edoxaban (OR 0.38; 95% CI, 0.26–0.54), rivaroxaban (OR 0.27; 95% CI, 0.18–0.42), and Watchman (OR 0.36; 95% CI, 0.16–0.80)—significantly decreased the risk of any stroke or systemic embolism. In the results, number of trials and sample size were not reported. Compared with VKA, use of individual NOACs—apixaban (1 RCT, n=19,740; OR 0.89; 95% CI, 0.80–0.99), dabigatran (2 RCTs, N=24,135; OR 0.90; 95% CI, 0.82–0.99), and edoxaban (2 RCTs, N=28,141; OR 0.89; 95% CI, 0.82–0.96)—significantly decreased all-cause mortality. However, no significant differences were noted in major extracranial bleeding and intracranial bleeding between Watchman, VKS, aspirin, and NOACs. This study was limited by the inclusion of studies that tested different doses of medication, did not report a CHADS2 score, and did not adjust for antiplatelet use that potentially affected bleeding rates. In addition, two trials in the review were included in the meta-analysis above. EBP

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Are women with a history of sexual trauma at an increased risk of developing chronic pelvic pain compared with women without this history?

EVIDENCE-BASED ANSWER

Yes, women with a history of sexual trauma are at higher risk for chronic pelvic pain (SOR: **B**, meta-analysis of cohort and case control studies, individual cohort studies.) The American College of Obstetrics and Gynecology acknowledges sexual trauma as a risk factor for chronic pelvic pain in women of all ages (SOR: **C**, expert opinion).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2006 meta-analysis of 122 cohort and case–control trials examined premenopausal and postmenopausal women with dysmenorrhea, dyspareunia, and noncyclical pelvic pain (N=64,286) to determine risk factors associated with each symptom.[1] Forty cohort studies focused on women with noncyclical pelvic pain and included comparison groups of individuals without pain. A primary outcome examined whether adult lifetime exposure to sexual abuse was associated with the development of chronic pelvic pain (CPP). History of sexual abuse had a significant relation to CPP (11 studies, N=1,630; odds ratio 3.5; 99% CI, 2.5–483). Major limitations of this study were its diagnostic criteria of "noncyclical pelvic pain" now called chronic pelvic pain, use of older studies, and inclusion of confounding variables (such as depression and anxiety), which could have been related to a history of sexual abuse.

A 2021 observational study (n=61) examined the relationship between sexual violence and chronic pelvic pain at a gynecology outpatient clinic.[2] The average age of women surveyed was 37 years with an average of a middle school education (51%) whose occupation was a housewife (66%). Thirty-three patients (54%) endorsed symptoms of CPP, with 11 (18%) admitting to suffering sexual abuse within their lifetime. Patients with a history of sexual abuse had a significantly higher risk of having CPP than those without such a history (OR 12; 95% CI, 1.4–99).

A 2013 retrospective chart review of urogynecology patients (n=1,899) examined the relationship between pelvic floor disorders and a history of sexual abuse.[3] The patients on average were 54 years of age, Hispanic, and noted to have an average BMI of 30.3 kg/m^2. Non–English-speaking patients were excluded. Out of a total of 1,260 women (66%), the prevalence of sexual abuse history was 213/1,260 (17%). CPP was significantly associated with a history of sexual abuse (OR 2.2; 95% CI, 1.2–3.8). The study also found that woman with CPP had a higher rate of depression (31% vs 12%; $P<.001$), anxiety (36% vs 13%; $P<.001$), and tobacco use (29% vs 14%; $P<.001$). A major limitation of this review was patients had been asked only one question to determine a history of sexual trauma. This question did not expand on the definition of sexual trauma to include "the type, nature, timing, duration, or extent of abuse" suffered by the patient.

A 2020 American College of Obstetrics and Gynecology (ACOG) practice bulletin focused on the clinical management of chronic pelvic pain.[4] ACOG defined chronic pelvic pain as discomfort "perceived to originate from pelvic organs/structures typically lasting more than 6 months" in duration. ACOG listed sexual abuse as a common condition associated with CPP. Referring patients for sexual or cognitive behavioral therapy either alone or in combination with myofascial management was part of the recommended treatment (level B recommendation based on limited or inconsistent scientific evidence). EBP

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Are gabapentinoid medications effective vs. placebo for pain control in adult patients with fibromyalgia?

EVIDENCE-BASED ANSWER

Yes. Gabapentin and pregabalin significantly decrease pain in the treatment of fibromyalgia (SOR: **A**; meta-analyses of randomized controlled trial [RCTs]). Duloxetine may be more effective, but it has a higher dropout rate than pregabalin (SOR: **B**. single RCT).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2009 meta-analysis of six randomized controlled trials (RCTs) (N=3,478 adults) with a median treatment duration of 11 weeks compared the efficacy of gabapentin and pregabalin with placebo as a method of pain control in the treatment of fibromyalgia.[1] Patients assigned to the experimental groups received either gabapentin dosed from 1,200 to 2,400 mg/day or pregabalin dosed from 150 to 600 mg/day. The control groups received placebo pills. Compared with placebo, gabapentinoids reduced pain in patients with fibromyalgia to a small degree (standardized mean difference [SMD], –0.28; 95% CI, –0.36 to –0.20). The number needed to treat (NNT) for a 30% or greater reduction in pain was 8.5 (95% CI, 6.4–12.6). Furthermore, when compared with placebo, gabapentin and pregabalin significantly improved sleep function (SMD –0.39; 95% CI, –0.48 to –0.29), anxiety (SMD –0.18; 95% CI, –0.27 to –0.10), health-related quality of life (SMD –0.30; 95% CI, –0.46 to –0.15), and fatigue (SMD –0.16; 95% CI, –0.23 to –0.09) on validated scales. Gabapentinoids were associated with a greater risk of withdrawal from the studies because of adverse events including dizziness, somnolence, weight gain, peripheral edema, and negative neurocognitive effects. External validity of the studies was limited due to the exclusion of patients with severe mental illness or somatic disorder. Furthermore, generalizability could be affected due to most participants being White female participants.

A 2017 meta-analysis, which provided an update to the 2009 study above, included eight RCTs (N=2,480) and had a median therapy phase of 13 weeks.[2] It compared the efficacy and safety of pregabalin, gabapentin, lacosamide, and levetiracetam with placebo in the treatment of pain in patients with fibromyalgia. Patients assigned to treatment groups were given an anticonvulsant of any dosage given by any route, and the control group received placebo medication. The meta-analysis found that pregabalin had a modest benefit in reducing pain by 50% in patients with fibromyalgia when compared with placebo (RR 1.59; 95% CI, 1.33–1.90). More dropouts because of adverse events with pregabalin use than with placebo use were observed (RR 1.68; 95% CI, 1.36–2.07).

In a 2019 open label, randomized-clinical trial, 99 outpatient adult women diagnosed with fibromyalgia were assigned to either duloxetine 30 to 60 mg or pregabalin 75 to 150 mg per day for four weeks.[3] Patients were excluded in cases of having used duloxetine, pregabalin, gabapentin, or antidepressants within 12 weeks before the study. Patients initially received either duloxetine (30 mg daily) or pregabalin (75 mg daily), which were titrated up to 60 mg duloxetine once daily and 75 mg pregabalin twice daily (150 mg daily) if the patient was tolerant and no serious adverse events were observed at the one-week clinic visit. Primary outcomes were between-group differences in mean score changes from baseline to endpoint for Widespread Pain Index (WPI) and Beck Depression Inventory-II (BDI-II). The WPI measures the number of painful areas (score range = 0–19) on the patient's body over the last week prior to the assessment, whereas the BDI-II (score range = 0–63) assesses depression with higher scores indicating more severe depressive symptoms

over the previous two weeks. WPI scores improved with a statistically significant difference between the two different treatment arms, favoring duloxetine (SMD –2.32; 95% CI, –4.46 to –0.18). The dropout rate and cumulative incidence of nausea were significantly higher in the duloxetine arm compared with the pregabalin arm (duloxetine 41.67% vs pregabalin 20.5%; $P=.024$). Limitations included a relatively small and highly selected sample size using several exclusion criteria, short follow-up period, an open-label study with potential risks of bias, and variations in outcomes because of a high number of dropouts in both treatment arms. EBP

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Is oral misoprostol as safe and effective as vaginal misoprostol for cervical ripening in full-term women?

EVIDENCE-BASED ANSWER

Oral misoprostol leads to less uterine hyperstimulation with fetal heart rate changes than vaginal misoprostol for cervical ripening in full-term women (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Oral misoprostol does not seem to increase the overall risk of cesarean delivery but likely results in a two-hour increase in time to delivery compared with vaginal misoprostol (SOR: **B**, meta-analysis of RCTs and 2 inconsistent RCTs).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 meta-analysis of 61 randomized controlled trials (RCTs) (N=20,274) evaluated the efficacy and safety of low-dose oral misoprostol for induction of labor of which 33 trials (N=6,110) compared with oral to vaginal dosing.[1] The reviewers considered any RCT comparing vaginal with oral misoprostol at an initial dose of 50 μg or less for the induction of labor in the third trimester of pregnancy. The most common oral dose was 50 μg every three to six hours, and vaginal dosing was roughly equally split between 25 μg and 50 μg. Almost all studies excluded women with previous uterine scarring, approximately half excluded women with ruptured membranes, and several excluded women with a Bishop score of greater than six. The primary outcomes measured were vaginal birth within 24 hours, cesarean deliveries, and uterine hyperstimulation, resulting in fetal heart rate changes. Oral misoprostol resulted in fewer vaginal deliveries within 24 hours of administration (16 trials, N=3,451; relative risk [RR] 0.81; 95% CI, 0.68–0.95; $I^2=87\%$) and an increased mean time to delivery of 1.9 hours compared with vaginal misoprostol (11 trials, N=1,734; 95% CI, 0.54–3.3 hours; $I^2=83\%$). Oral misoprostol did not change the overall rate of cesarean deliveries (32 trials, N=5,914; average RR 1.0; 95% CI, 0.86–1.2; $I^2=47\%$) but did result in fewer cesarean deliveries for indication of fetal distress (24 trials, N=4,775; RR 0.74; 95% CI, 0.55–0.99; $I^2=44\%$) and less uterine hyperstimulation with fetal heart rate changes (25 trials, N=4,857; RR 0.69, 95% CI, 0.53–0.92; $I^2=29\%$). There was no difference in other secondary maternal outcomes (nausea, vomiting, infection, or postpartum hemorrhage)

or neonatal outcomes (APGAR score, neonatal intensive care unit admission, or meconium staining). This meta-analysis was limited by substantial heterogeneity in several different outcomes that was not resolved when excluding lower quality trials.

A 2022 RCT (n=200) at a hospital in Hayatabad, Pakistan, compared the effectiveness of oral versus vaginal misoprostol for induction of labor.[2] Researchers included pregnant women at term (>37 weeks' gestation) with a single, viable fetus in cephalic presentation who required induction of labor and excluded women with severe systemic disease (eclampsia, cardiac, renal, or hepatic disease) or previous uterine surgery. Women received 50 μg of oral misoprostol or 25 μg of misoprostol into the posterior vaginal fornix. Doses were repeated every four hours until either active labor was achieved, the cervix was suitable for amniotomy, or a maximum of five doses. Approximately half of the women in each group were primiparous, and the most common indications for induction in both groups were postdates, premature rupture of membranes, and pregnancy-induced hypertension. Primary outcomes included induction-to-delivery interval and effectiveness of labor induction (defined as active labor within 24 hours of last dose). Mean induction-to-delivery interval was lower in the oral misoprostol group (19 vs 23 hours, $P=.0001$); however, overall effectiveness to induce labor was greater in the vaginal group than in the oral group (88% vs 80%; statistical analysis not reported). Cesarean delivery rates were not reported.

Another 2022 RCT (n=100) at a medical center in Karwar, India, compared oral and vaginal misoprostol for induction of labor.[3] Patients had a term gestation with a single, viable fetus in cephalic presentation with reactive fetal heart tracing and intact membranes or ruptured for less than four hours. Women with previous uterine surgery, active herpes simplex infection, chorioamnionitis, or Bishop score greater than four were excluded. Both groups received 50 μg of misoprostol every four hours, either orally or in the posterior vaginal fornix until in active labor or a maximum of six doses were administered. The average gestational age was 39 weeks, and there was a higher percentage of primigravid patients in the oral group than in the vaginal group (60% vs 48%; statistical analysis not reported). Most patients (88 of 100) were induced for pregnancy with hypertension. Outcome measures included successful induction (active labor within 24 hours of initial dose), induction-to-delivery interval, and mode of delivery. More women were successfully induced in the vaginal group (43 of 50) compared with the oral group (35 of 50), and the median induction-to-delivery interval for women who delivered within 24 hours was 16 hours in the oral group compared with 9.6 hours in the vaginal group (comparison statistics not given). A total of 15 women in the oral group underwent cesarean delivery compared four women in the vaginal group. The randomization process was not described clearly, and there were apparent errors noted in calculating the percentages of the results. EBP

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Does the baby-led weaning feeding strategy decrease choking incidents in children younger than 18 months old?

EVIDENCE-BASED ANSWER

It is not clear. Baby-led weaning does not seem to decrease choking incidents in children younger than 12 months old (SOR **A**; 2 randomized controlled trials and 1 cross-sectional study). However, when choking episodes are examined based on food type, fewer choking incidents are observed with finger food and lumpy puree for baby-led weaning compared with traditional weaning (SOR: **B**, 1 cross-sectional study).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2018 randomized controlled study (n=280) assessed the effects of baby-led weaning on choking, infant growth, and iron levels.[1] Babies, five to six months old and breast-fed, were randomly assigned to the baby-led weaning group (BLW, n=142) or the traditional spoon feeding group (TSF, n=138). Researchers excluded infants born before 38 weeks of gestation, less than 2,500 g at birth, or planned formula use. All families received seven well-child care visits up to age 12 months. The BLW group also attended group training meetings, participated in six home visits for support and education in BLW and received food lists. On a weekly basis, parents completed a phone interview and reported the occurrence of choking and type of food responsible. No difference in choking episodes was observed between the BLW group and the TSF group (risk ratio [RR] 0.62; 95% CI, 0.11–3.7). Raw apple and raw carrots were the two foods that caused two and three choking events, respectively. Generalizability to formula-fed babies limited the study validity.

A 2016 blinded randomized controlled trial (n=206) evaluated the impact of baby-led weaning on infant choking and gagging.[2] Babies born after 37 weeks' gestation were randomized to Baby-Led Introduction to SolidS (BLISS, n=105) or control (traditional feeding practices, n=101). BLISS is a modified form of baby-led weaning that provides resources and support addressing concerns about choking risk from antenatal care to 9 months old. Exclusion criteria applied before birth were pregnant women whose first prenatal appointment was after 34 weeks' gestation, who were less than 16 years old, or who did not plan to live locally for the next two years. Exclusion criteria applied after birth were premature birth (<37 weeks' gestational age) or presence of a congenital abnormality that would likely affect feeding or growth. Follow-up was at 6, 7, 8, 11, and 12 months of age. Parents reported frequency of choking using questionnaire at each follow-up period. No difference in choking was observed between the BLISS and control groups for any age (RR 1.01; 95% CI, 0.73–1.4). Parental recall and identification of choking episodes and generalizability to all socioeconomic levels limited study validity.

A 2017 retrospective cross-sectional study (n=1,151) assessed the effect of weaning style on episodes of choking.[3] Mothers with babies introduced to solid foods by 12 months of age self-reported the weaning process as strict baby-led weaning (n=412), loose baby-led weaning (n=377), or traditional (n=362.) The study excluded mothers who could not consent and mothers of babies with substantial health issues that could be related to diet of physical development. Data on choking frequency, ever choked and food type (finger food, lumpy puree, and smooth puree), were collected by using a questionnaire. No significant association was observed between weaning style and ever choking for all food types. Strict and loose baby-led weaning resulted in fewer choking episodes compared with traditional weaning for finger foods (mean frequency, strict 1.6%, loose 1.2%, traditional 1.8%; P=.014) and lumpy puree (mean frequency, strict 0.32%, loose 0.54%, traditional 1.2%; P=.002). No significant difference in choking episodes was observed between the three weaning groups for smooth puree. Limitations included online questionnaire design potentially leading to selection bias, self-selection bias of participants with understanding of baby-led weaning, and potential for recall bias. EBP

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Does stress management improve outcomes in patients with heart disease?

EVIDENCE-BASED ANSWER

Stress management interventions seem to modestly decrease coronary heart disease (CHD)-associated mortality (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]) but do not demonstrate statistically significant effects on other clinical endpoints. Additionally, application of stress management interventions consistently produces small-to-moderate improvements in mental health outcomes in those with CHD (SOR: **A**, meta-analyses of RCTs).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2017 systematic review and meta-analysis of 35 randomized controlled trials (RCTs; N=10,703) assessed the effectiveness of psychological interventions compared with usual care for individuals with coronary heart disease (CHD) on mortality (total and cardiac-specific), cardiac morbidity, and participant-reported psychological outcomes.[1] This review included adults with and without underlying psychopathology after myocardial infarction (MI), cardiac revascularization procedures, percutaneous coronary intervention, or with angina or angiographically identified coronary artery disease. Studies with a majority of patients with other cardiac conditions (eg, atrial fibrillation or congestive heart failure) were excluded. The review included a variety of psychological interventions including relaxation, self-awareness and self-monitoring, emotional support, and cognitive restructuring. The interventions often addressed specific mental health targets (stress, anxiety, depression, etc) and were applied by a range of mental health professionals, with follow-up ranging from six months to 10.7 years. The controls were provided usual care. Medical and psychological outcomes were reported. Psychological intervention was found to decrease CHD mortality (11 trials, N=4,792, relative risk [RR] 0.79; 95% CI, 0.63–0.98, number needed to treat [NNT]=56) but not total mortality, rates of revascularization, or nonfatal MI. Intervention did significantly decrease depression, anxiety, and stress in these patients (19 trials, N=5,825, standardized mean difference [SMD] –0.27; 95% CI, –0.39 to –0.15; 12 trials, N=3,161, SMD –0.24; 95% CI, –0.38 to –0.09; 8 trials, N=1,251, SMD –0.56; 95% CI, –0.88 to –0.24, respectively). No harms of the intervention were noted. Limitations of this review included significant statistical heterogeneity for the self-reported psychological outcomes but not for the clinical outcomes. The quality of evidence varied by outcome but ranged from very low to moderate.

A 2020 systematic review and meta-analysis of nine RCTs (N=644) assessed the effects of mindfulness-based interventions (MBIs) on patients with CHD.[2] Patients included in the meta-analysis were adults who had had an MI or revascularization procedure(s) or had angina or CHD on angiography. The MBIs varied and included mindfulness-based stress reduction, mindfulness-based cognitive therapy, mindfulness meditation, and mindfulness-based art therapy. The number of sessions offered ranged from three to 31 sessions and lasted from one week to one year. When compared with an inactive control, the meta-analysis found that MBIs significantly reduced depression (7 RTCs, N=370, SMD –0.72; 95% CI, –1.2 to –0.21) and stress (3 studies, N=150, SMD –0.67; 95% CI, –1.0 to –0.34) but had no significant impact on anxiety (7 studies, N=370, SMD –0.42; 95% CI, –1.2 to 0.33). Mindfulness-based

interventions did not show a significant effect on systolic blood pressure (2 studies, N=60, SMD –0.48; 95% CI, –1.9 to 0.93) or diastolic blood pressure (2 studies, N=60, SMD –0.25; 95% CI, –0.76 to 0.26). No harms of this interventions were reported. When MBI was compared with an active control (included muscle relaxation, physical exercise, stress inoculation training, or self-help), there was no significant effect found on depression, stress, anxiety, blood pressure, or physical quality of life. The review was limited by the heterogeneity in the type, frequency, and duration of MBI training. EBP

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In adults with migraines, does daily topiramate reduce the number of migraine days?

EVIDENCE-BASED ANSWER

Topiramate reduces episodic migraine headaches by about one headache day per month compared with placebo at four or more weeks of treatment (strength of recommendation [SOR]: **A**, meta-analyses of randomized controlled trials [RCTs]). However, there may not be a significant difference in mean headache days between treatment with topiramate compared with amitriptyline for episodic migraines (SOR: **C**, small RCT). Topiramate may also significantly reduce headache days per month compared with placebo in patients with chronic daily headaches (SOR: **C**, small RCT).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2015 systematic review and network meta-analysis of 179 randomized controlled trials (RCTs) compared the efficacy of various drugs for the prophylactic treatment of migraines (N=15,493 in trials comparing with placebo).[1] The studies averaged 112 patients (average age 39.2 years old, and 78% women). The review included adults with migraine headaches of at least four weeks' duration, and 120 trials studied episodic migraine headaches (<15 days/month, average 5.6 headaches per month). The meta-analysis included 12 trials that compared topiramate doses (50, 100, and 200 mg) with placebo at 4 to 24 weeks in patients with episodic migraines with a range of headaches per month of 4.5 to 11.7. Eleven of the trials (N=2,728) used frequency (headache days per month) as the outcome. Pooled results showed that topiramate was better than placebo at reducing headache days per month in patients with episodic migraines at all time points (4–24 weeks) and all doses. The mean difference (MD) was –1.1 headache days (95% CI, –1.5 to –0.79) at four weeks of treatment, –1.3 headache days (95% CI, –1.9 to –0.7) at eight weeks, and –0.99 headache days (95% CI, –1.3 to –0.64) at 12 weeks.

A 2013 Cochrane review of 10 RCTs examined the use of topiramate (N=893) versus placebo (N=893) for the prevention of episodic migraine headache in adults.[2] The review included studies with patients who had episodes of migraine headaches separated by migraine-free days and specifically excluded studies examining tension-type headache, chronic migraine, and transformed migraine. The studies included patients who received topiramate in doses from 50 to 200 mg per day versus placebo, and outcomes were measured over a range of 4 to 52 weeks with a mean treatment time of 19 weeks. Nine other studies included in the review examined the dose–effect of topiramate. Patients who received topiramate had 1.2 fewer headache days per month compared with placebo (MD –1.2; 95% CI, –1.6 to –0.80). The studies that looked at dose–effect versus placebo did not show a difference at 50 mg daily (MD –0.95; 95% CI, –1.95 to 0.04) but did show decreased headache days per month at both 100 mg (MD –1.15; 95% CI, –1.6 to –0.71) and 200 mg daily (MD –0.94; 95% CI, –1.5 to –0.36).

A 2008 single-center RCT (N=63) compared efficacy of topiramate versus amitriptyline versus both for treatment of chronic episodic migraine headaches.[3] Adults patients 18 to 60 years old with migraines, with or without aura, average 3 to 12 migraine days per month, were randomized to one of the treatment groups. Those with >15 migraine days/month and those using ergots or triptans for acute treatment were excluded. Medications were titrated over eight weeks to maximum tolerated dose (up to 200 mg/day topiramate or 150 mg amitriptyline). Data were collected at eight weeks and again after a four-week maintenance period. At 12 weeks, improvements in mean frequency of headaches days per month were noted for all groups: topiramate alone (0.65/month vs 6.30/month), amitriptyline alone (0.91/month vs 6.09/month), and both (0.95/month vs 6.05/month). No significant difference in mean frequency of headaches days per month was noted between groups. Side effects were greatest in the combination group (42.9%, vs 15% for topiramate and 22% for amitriptyline).

A 2003 single-center RCT (n=27) from Italy examined topiramate for chronic daily headaches compared with placebo.[4] The mean age was 43 years old for the topiramate group (n=13) and 44 years old for placebo (n=14). Patients who were pregnant or lactating, had renal stones or neurological diseases, or were on carbonic anhydrase inhibitors or migraine prophylaxis were excluded. The intervention group received topiramate 50 mg daily for eight weeks; the control group received placebo. The primary outcome was the mean number of headaches per 28 days, which was significantly lower in the topiramate group at eight weeks compared with baseline and the placebo group at eight weeks (8.1 vs 20.9; $P<.0007$; and vs 20.6; $P<.0005$, respectively). This RCT did not evaluate topiramate use as a first-line prophylactic regimen for chronic daily migraines in prophylaxis-naive patients. EBP

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Do carbohydrate-restrictive/keto diets, compared with moderate/high carbohydrate diets, increase all-cause and cause-specific mortality?

EVIDENCE-BASED ANSWER

The quality and source of the carbohydrate may affect mortality more than the amount of carbohydrate in the diet. Compared with moderate-carbohydrate intake, low-carbohydrate diets containing more animal-derived fats or protein are associated with up to a 20% increased mortality risk, whereas plant-based diets are associated with up to an 18% decreased mortality risk (SOR: **B**, meta-analysis of observational studies and large cohort study). Furthermore, low-carbohydrate diets high in refined grains, added sugars, and more processed foods are associated with higher mortality risk compared with those high in whole grains and natural foods (SOR: **B**, large cohort study).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2018 cohort study (n=15,428) and meta-analysis (8 cohort studies; N=432,179) investigated a potential association between dietary carbohydrate intake and all-cause mortality.[1] The cohort study included adults (45−64 years old) in four different U.S. communities and excluded patients with extreme caloric intakes (ie, <500 or >3,500 calories for women; <600 or >4,200 calories for men). Researchers followed patients across six visits spanning 30 years. Patients completed a questionnaire at each visit quantifying the frequency that different foods were consumed. A scoring system helped classify patients' diets based on how low carbohydrate, animal based, or plant based they were. The primary outcome was all-cause mortality, assessed by telephone calls, local hospital and state health department records, and the National Death Index. Researchers attempted to account for differences in age, sex, race, community location, education level, cigarette smoking status, physical activity level, total energy intake, and diabetes status in assessing all-cause mortality. For the meta-analysis, data from this cohort study were combined with data from seven other prospective cohort studies. The results for both the cohort study and the meta-analysis similarly showed a U-shaped association between carbohydrate intake and mortality, with an increased mortality risk associated with both high (hazard ratio [HR] 1.2; 95% CI, 1.1–1.3) and low (HR 1.2; 95% CI, 1.1–1.4) carbohydrate consumption compared with moderate carbohydrate consumption. When evaluating animal- versus plant-based food sources, animal-based foods were associated with an increased mortality risk (HR 1.2; 95% CI, 1.1−1.3), whereas plant-based foods were associated with a decreased mortality risk (HR 0.82; 95% CI, 0.78−0.87). This study was limited by its observational nature and the intermittent assessment of diet that may not have accounted for many changes over time.

A 2021 prospective cohort study (n=93,654) evaluated if dietary carbohydrate intake or animal versus plant sources of protein and fat in the diet was associated with mortality risk.[2] Patients included adults (40–69 years old) in Japan. Researchers excluded patients with a history of cancer, stroke, ischemic heart disease, or chronic liver disease. All patients answered a questionnaire at baseline and again at five and 10 years, with questions about medical history, smoking, drinking, and dietary habits. Researchers scored patients' diets using the low carbohydrate diet score, giving higher scores to patients with intake of more fat and protein and less carbohydrate, and divided patients into quintiles. Furthermore, they performed a subgroup analysis based on whether dietary components were animal or plant based. The primary outcome was all-cause mortality, confirmed by death certificate. A weak, U-shaped association was noted between dietary carbohydrate score and risk of total mortality, with the lowest risk among patients in quintiles 3 and 4. HRs for each quintile were as follows (from highest carbohydrate intake [reference] to lowest): 1.0, 0.95, 0.93, 0.93, and 1.9. The mortality association was similar when looking only at animal-based diets, but plant-based diets showed a stronger inverse association with carbohydrate intake (for lowest carbohydrate intake vs highest HR 0.89; 95% CI, 0.83–0.94). Limitations included those inherent to observational studies, only assessing diet at baseline and not accounting for changes over time and patients all being older and Japanese that may limit applicability to other populations.

A 2020 prospective cohort study (n=37,233) investigated the association between low-carbohydrate

diets and mortality among U.S. adults.[3] Researchers analyzed data from the U.S. National Health and Nutrition Examination Survey (NHHES) between 1999 and 2014, including patients at least 20 years old and excluding those with very low or high caloric intake (similarly defined as the first study above). Dietary data from the NHHES were analyzed based on percentage of energy from each macronutrient and a scoring system was used to quantify how closely a person's diet resembled a low carbohydrate diet. An additional scoring system quantified "healthy" versus "unhealthy" carbohydrates and fats. Examples of "healthy" carbohydrates were whole grains, non-starchy vegetables, and whole fruits. The primary endpoint was all-cause mortality ascertained from the National Death Index. Researchers performed statistical analysis adjusting for potential confounding factors such as age, sex, race/ethnicity, educational level, family income, smoking, alcohol drinking, physical activity, total energy intake, body mass index, family history of diabetes and heart disease, and histories of diabetes, heart disease, and cancer. The amount of carbohydrate in the diet was not associated with all-cause mortality but rather the quality of carbohydrates in the diet was. A higher mortality association with unhealthy low-carbohydrate diets (HR 1.1, CI 1.0–1.1) compared with healthy low-carbohydrate diets (HR 0.91, CI 0.87–0.95) was noted. This study was also limited by its observational nature and only assessing diet at baseline by patient questionnaire. EBP

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Is virtual screening for cognitive impairment using validated screening tools as accurate as in-person assessment in older adults?

EVIDENCE-BASED ANSWER

Probably not. Remote screening tools have a sensitivity between 41% and 100% and specificity between 75% and 100% compared with in-person assessment (SOR: **B**, systematic review of cross-sectional studies). In-person screening with a 22- or 30-point Montreal Cognitive Assessment (MoCA) has a sensitivity of 70% to 79% and a specificity of 69% to 77%, whereas the 22-point telephone MoCA has a sensitivity of 72% and specificity of 59% (SOR: **B**, cohort study).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2022 Cochrane review of 31 cross-sectional studies (N=3,075) examined virtual dementia screening (telephone or video).[1] Of these 31 studies, seven (6 telephone and 1 video study, N=756) compared the accuracy of virtual dementia screening against a clinical diagnosis of dementia. Patients had a mean age of 73 years old, with 44% to 77% female. Telephone assessments included the Telephone-Free-Cog, the Adult Lifestyles and Function Interview–Mini-Mental State

TABLE. Sensitivity and specificity of remote screening tests for dementia, with in-person assessment used as the gold standard[1]

Test	Trials (patients)	Score[a] range	Threshold	Sensitivity % (95% CI)	Specificity % (95% CI)
ALFI-MMSE, telephone	2 (133)	0–26	16 or less	100 (95–100)	75 (63–84)
			17 or less	67 (54–78)	100 (90–100)
IMCT, telephone	1 (132)	0–37	From 17 if illiterate to 23 with college	80 (68–89)	81 (69–89)
SPMSQ, telephone	1 (100)	0–10	≤5	41 (29–54)	97 (85–100)
Telephone-Free-Cog	1 (107)	0–24	≤19	87 (74–94)	100 (94–100)
Rowland Universal Dementia Assessment Scale, video	1 (42)	0–30	≤23	80 (44–97)	91 (75–98)

[a] Higher scores indicate better cognitive function. ALFI-MMSE, adult lifestyles and function interview mini-mental state exam; IMCT, information memory concentration test; SPMSQ, short portable mental status questionnaire.

Examination (ALFI-MMSE), the Short Portable Mental Status Questionnaire (SPMSQ), and the information memory concentration test (IMCT). The video assessment was the Rowland universal dementia assessment scale. Overall, in assessing the accuracy of remote assessment tools, sensitivity of remote tools was between 41% and 100%, and specificity was between 75% and 100% for a diagnosis of dementia (see **TABLE**). Individual studies were generally small.

A 2020 cohort study (n=428) compared the accuracy of in-person and virtual assessments among older adults.[2] Patients had a mean age of 78.1 years old, with 66% female and 54% non-White. The original Montreal Cognitive Assessment (MoCA)-30 (score range 0–30) and MoCA-22 (a shortened version of the MoCA-30, score range 0–22) were used for in-person assessment, whereas the telephone MoCA (or T-MoCA, score range 0–22) was used for virtual assessment. To identify mild cognitive impairment (MCI), the Youden's index optimal cut score of 22 for the MoCA-30 and score of 17 for both MoCA-22 and T-MoCA was used. The MoCA-30 had a sensitivity of 70% and specificity of 77%. The MoCA-22 had a sensitivity of 79% and a specificity of 69%. The T-MoCA had a sensitivity of 72% and specificity of 59%. Using ROC analysis, the T-MoCA had a significantly lower diagnostic accuracy for MCI compared with the MoCA-22 (AUC, 0.71 vs 0.79; $P=.002$) and MoCA-30 (AUC, 0.71 vs 0.80; $P=.003$), whereas the in-person MoCA-22 and MoCA-30 tests did not significantly differ from each other ($P=.23$). This study was limited because the T-MoCA was not validated against other widely used telephone screens. In addition, the cross-sectional approach was not as sensitive compared with longitudinal studies in detecting cognitive changes. EBP

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Is pramipexole an effective adjunctive treatment for treatment-resistant depression?

EVIDENCE-BASED ANSWER

Pramipexole seems to be a safe and effective treatment option for unipolar and bipolar depression, either as monotherapy or as adjunctive treatment, with a number needed to treat for clinical response of 5.6 (SOR: **B**, meta-analysis of randomized controlled trial s). Pramipexole may have a response rate of up to 74% among patients with treatment-resistant unipolar or bipolar depression (SOR: **C**, single observational study).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

Pramipexole is a dopamine receptor agonist that is approved by the Food and Drug Administration in the treatment of Parkinson disease and restless leg syndrome and has been studied as an off-label, adjunctive option in treatment-resistant depression.

A 2019 systematic review and meta-analysis (13 studies; N=504) looked at effectiveness of pramipexole for treatment of unipolar and bipolar depression.[1] Patients were at least 18 years old (mean age 45 years old; 57% female) with major depressive disorder (MDD) or bipolar disorder with depression (diagnosed using Diagnostic and Statistical Manual of Mental Health Disorders, 4th edition [DSM-4] criteria). Researchers excluded studies looking at patients with comorbid significant medical diagnoses. The intervention was pramipexole either as monotherapy or as augmentation, with flexible dosing based on clinical response (mean maximum dose of 1.6 mg daily). The comparison in the randomized controlled trials (RCTs) was placebo. All patients could be on additional antidepressant or mood stabilizing medications. The primary outcome was treatment response, defined as 50% reduction from baseline score assessed using various clinician-administered depression assessments. Secondary outcomes included remission rate, defined as a subthreshold score on a depression assessment. Researchers followed patients for 6 to 12 weeks. Based on the pooled RCT data, patients treated with pramipexole had a response rate of 41%, which was superior to placebo (4 RCTs, N=277; RR 1.8; 95% CI, 1.1–2.8; number needed to treat [NNT]=5.6). No significant improvement was observed in remission rates with pramipexole treatment. Pramipexole did have a higher rate of nausea when compared with placebo (odds ratio 2.8; 95% CI, 1.5–5.3), but the frequency of all other adverse events were similar between groups. Limitations included heterogeneity in diagnostic criteria, medication dosing, and outcome measures affecting applicability, as well as small study number and sizes.

A 2022 retrospective cohort study (n=116) aimed to evaluate the effectiveness of pramipexole augmentation in treatment-resistant depression.[2] Researchers included patients at least 18 years old in the outpatient setting who met the DSM-5 diagnostic criteria for bipolar I (BD-I), bipolar II (BD-II), or MDD and failed previous treatment with at least two antidepressants of different classes. The study excluded those with psychotic depression, rapid cycling bipolar disorder, or a previous failure with pramipexole therapy. Based on clinical response, the dose was started at 0.18 mg/d and titrated up by 0.18 mg/d every week to a maximum dose of 2.1 mg/day (median dose 1.05 mg/day). Patients continued to receive their preexisting antidepressant or mood stabilizing therapy. No comparison or control group was present. The primary outcome was depression remission rate, defined as a normal score (<7) on the Hamilton Depression Rating Scale (HDRS) after 24 weeks of therapy. The secondary outcome was therapeutic response, defined as a decrease in HDRS score of at least 50% from baseline. After 24 weeks of pramipexole treatment, 74% of patients had achieved therapeutic response and 66% of patients had achieved remission. By study end, 8.6% of patients dropped out, mostly because of side effects such as somnolence, transient hallucinations, confusion, anxiety, or lower extremity edema. EBP

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What is the most sensitive and specific imaging technique for identifying pheochromocytomas?

EVIDENCE-BASED ANSWER

Gallium-based radionuclide (^{68}Ga-DOTA-SST) positron emission tomography/computed tomography (CT) has the highest sensitivity of all functional imaging techniques for detecting pheochromocytomas (SOR: A, systematic review of diagnostic cohort studies). With unenhanced CT or magnetic resonance imaging, the combination of lesion lipid content and size is the most predictive of pheochromocytomas (SOR: **B**, retrospective cohort study).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2019 meta-analysis of 13 diagnostic cohort studies assessed the performance of gallium-labeled somatostatin receptor-targeting peptide positron emission tomography (^{68}Ga-DOTA-SST PET) in detecting pheochromocytomas and paragangliomas (PPGL) as compared with histopathologic results or best value comparator (a combination of computed tomography [CT]/magnetic resonance imaging [MRI], clinical, or biologic studies).[1] Nine of these studies met the inclusion criteria and underwent quantitative analysis (N=215 patients) for patients with PPGLs who received functional imaging for detection of their tumor. These studies included a ^{68}Ga-DOTA-SST PET and three other functional radionuclide imaging techniques currently approved by the Food and Drug Administration for imaging pheochromocytoma. The pheochromocytoma detection rate using ^{68}Ga-DOTA-SST PET was the primary outcome and comparing rates with other functional imaging was the secondary outcome. The per-lesion pooled-detection rate for ^{68}Ga-DOTA-SST compared with best value comparator was 93% sensitive (9 studies, N=998; 95% CI, 0.91–0.95; I^2=26%), which was higher than other radionuclide imaging techniques: fluorine-18-l-dihydroxyphenylalanine (80% sensitive), fludeoxyglucose F18 (74% sensitive), and iodine-131 meta-iodobenzylguanidine (38% sensitive). Exceptions potentially included genetic subtypes of PPGLs because half the studies did not include genetic tests. In addition, one study showed ^{68}Ga-DOTA-SST sensitivity decreased to 35% (n=14) if the patient had a rare polycythemia/paraganglioma syndrome.

A 2022 retrospective multicenter study of 13 tertiary academic hospitals proposed a predictive model to distinguish pheochromocytomas from other adrenal tumors on CT without contrast (unenhanced CT) or out-of-phase MRI.[2] Patients were categorized into two groups: (1) pheochromocytomas confirmed by histology (n=163) and (2) those without pheochromocytomas based on urinary or plasma metanephrines or catecholamine levels (n=968). All patients underwent CT or MRI to determine the primary outcome of developing a predictive model to rule out pheochromocytomas. Investigators found that with unenhanced CT at 16 Hounsfield Units (HU), there was a 90% sensitivity and 96% specificity for the detection of pheochromocytomas. They also found that larger lesions were most likely to be pheochromocytomas (area under the receiver-operator characteristic curve [AUC] 0.834) with lesions <20 mm most likely adenomas. In addition, lesions with a low lipid content identified on CT were most likely pheochromocytomas (AUC 0.917), and lesions with a higher lipid content are predictive of nonpheochromocytomas (89.7% sensitivity and 95.9% specificity). The combination of tumor size and lipid content had a sensitivity of 88.1% and specificity of 99.2% (AUC 0.961). The combination of the two predictors in the context of patients with dyslipidemia and obesity had a slight increase in sensitivity (89.9%) and specificity (92.1%) (AUC 0.970). CT was similarly sensitive but more specific than MRI (AUC 0.757) with a 90.3% sensitivity and a 61.0% specificity. Limitations of this study included its retrospective design and using imaging and biochemical reference ranges that varied between institutions. EBP

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Is sickle cell trait associated with exertional rhabdomyolysis in adults?

EVIDENCE-BASED ANSWER

The risk of developing exertional rhabdomyolysis is 50% higher in those with sickle cell trait (SCT) in comparison with those without SCT, especially in patients with an elevated body mass index, or using tobacco, statin medications, or antipsychotics (SOR: **B**, a single retrospective cohort study). Implementing prevention strategies for exertional injuries for everyone, however, is preferred to SCT screening of athletes and military service members (SOR: **C**, expert opinion).

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A 2016 population-based, retrospective cohort study (n=47,944) of Black active-duty Army soldiers evaluated the relative risk of sickle cell trait (SCT) and exertional rhabdomyolysis.[1] The study used the Stanford Military Data Repository (SMDR), which contains comprehensive medical data on all Army active-duty soldiers, to select a cohort of Black soldiers who served between January 2011 and December 2014 with and without SCT. Using the electronic health record, all members of the cohort were screened using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for rhabdomyolysis (728.88) or myoglobinuria (791.3). To ensure all cases were exertional, the ICD-9-CM codes for drug toxicity events and various tissue traumas were excluded if within two days before or seven days after the rhabdomyolysis diagnosis. Of the 47,944 soldiers, 3,564 had SCT, and 391 cases of exertional rhabdomyolysis were identified (hazard ratio [HR] 1.5; 95% CI, 1.1–2.1). Other significant variables examined were body mass index (BMI), tobacco use, and prescription of statins or antipsychotics within the prior two months. A BMI greater than or equal to 30 kg/m^2 (HR 1.4; 95% CI, 1.0–1.9), female sex (HR 0.5; 95% CI, 0.38–0.67), tobacco use (HR 1.5; 95% CI, 1.2–1.9), a statin (HR 2.9; 95% CI, 1.5–5.6), and antipsychotic prescription (HR 3.0; 95% CI, 1.3–6.8) were associated with a greater risk of exertional rhabdomyolysis in patients with SCT. Of the 96 total deaths in the study, no increased risk of death was observed among soldiers with SCT. The only death from exertional rhabdomyolysis occurred in a soldier without SCT. A key limitation is difficulty generalizing results to the civilian population.

In 2021, the Consortium for Health and Military Performance hosted a summit on Exercise Collapse Associated with Sickle Cell Trait (ECAST). The American College of Sports Medicine, the American Medical Society for Sports Medicine, and the American Society of Hematology were represented.[2] The summit sought to consolidate expert opinion on athletes and military service members with SCT and make recommendations. The ECAST organizers acknowledged that SCT is associated with exertional rhabdomyolysis, but the summit recommended universal training precautions instead of universal screening. 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 reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

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Is psilocybin effective for treatment of depression?

EVIDENCE-BASED ANSWER

In patients with treatment-resistant or long-standing depression, one or two doses of psilocybin along with psychological support may reduce depression symptoms by 20% to 63% compared with placebo or no treatment and may be as effective as escitalopram (SOR: **B**, randomized controlled trials).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A double-blind multinational randomized controlled trial (RCT) evaluated the efficacy of psilocybin in 233 patients with treatment-resistant depression.[1] Patients were on average 39.8 years old, 52% female, and 92% White race. The majority (95%) had previous depressive episodes (mean 6.9 lifetime episodes), and 86% reported feeling depressed for more than one year at the time of study enrollment. All patients had depression meeting Diagnostic and Statistical Manual of Mental Disorders, 5th ed (DSM-V), criteria and treatment-resistant was defined as no response to two or more adequate (ie, both dose and duration) trials of standard antidepressant therapy. The study excluded patients at high-risk for suicide. The intervention consisted of a single dose of synthetic psilocybin at 25 mg (n=79) or 10 mg (n=75); patients in the control group (n=79) received 1 mg of psilocybin. Before the intervention, all patients were weaned off antidepressants and other central nervous system medications for at least two weeks. All patients received psychological support for six to eight hours after psilocybin administration. The primary outcome was the change from baseline to week three in the Montgomery–Åsberg Depression Rating Scale score (MADRS; range 0–60, higher scores indicating more severe depression). The mean MADRS score was 32.5 at baseline and was not significantly different between the three groups. Secondary outcomes included sustained response through 12 weeks and adverse events. At three weeks, the change in the MADRS score was greater in the 25 mg compared with 1 mg group (–12.0 vs –5.4; mean difference [MD] –6.6; 95% CI, –10.2 to –2.9) but was not significantly different in the 10 mg versus 1 mg group (MD –2.5; 95% CI, –6.2 to 1.2). No statistically significant differences were observed in sustained response at 12 weeks among the three groups. Patients given 25 mg of psilocybin had higher rates of adverse events than either the 10 mg or 1 mg groups (84%, 75%, and 72%, respectively; statistical significance not provided). The most common adverse events were headache and nausea; however, rates of suicidal ideation and intentional self-harm were low (1% or less) and were similar among the three groups. The study was limited by industry funding and the lack of an assessment of the patient's ability to guess the psilocybin dose they were given.

A 2021 double-blind RCT from the United Kingdom compared the efficacy and safety of psilocybin versus escitalopram in 59 patients with long-standing moderate-to-severe major depressive disorder (MDD).[2] Patients had a mean age of 41 years old, 34% were female, and 88% self-reported as White race. The majority were university-level educated (76%) and had moderate-to-severe depression based on a Hamilton Depression Scale (HAMD) score of at least 17 (range 0–52; higher scores indicating greater depression). The trial excluded patients with suicide attempts, a personal or family history of psychosis, and mental health or medical conditions making them unsafe or unsuitable for the trial. All patients discontinued any psychiatric medications for two weeks before starting the trial. Patients assigned to psilocybin received a single 25 mg PO dose at study entry which was repeated at three weeks; they also received PO

placebo capsules as escitalopram mimics. Patients assigned to escitalopram were given 10 mg PO daily for three weeks followed by 20 mg daily for an additional three weeks; these patients also received a single PO dose of 1 mg psilocybin (as placebo) at study entry and again at three weeks. Patients in both groups received ongoing supportive psychological therapy delivered by mental health professionals during the study. The primary outcome was the change at six weeks in the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16; score range 0–27; higher scores indicating greater depression), with a mean baseline score of 15. At six weeks, both psilocybin and escitalopram groups had similarly improved QIDS-SR-16 scores (–8 vs –6, respectively; MD –2, 95% CI, –5 to 0.9). Rates of adverse events were similar between the psilocybin and escitalopram groups (87% and 83%, respectively); the most common side effects were headache and nausea in both groups.

A 2021 open-label RCT from the United States evaluated the effectiveness of psilocybin-assisted therapy in 27 patients with MDD.[3] Patients were on average 40 years old with MDD diagnosed by DSM-V criteria. The mean illness duration was 21.5 years, with a current episode of depression lasting greater than two years. Two-thirds were women, and 92% were racially White. The study excluded patients with substance abuse, psychotic, and bipolar disorders. Patients randomized to the intervention group received two doses of PO psilocybin along with approximately 11 hours of supportive psychotherapy. The first dose was 20 mg/70 kg, and the second (11 days later) was 30 mg/70 kg. Patients in the control group were assigned to a waitlist. The primary outcome was the HAMD score at baseline, five, and eight weeks after enrollment (1 and 4 weeks after the second psilocybin treatment). Patients given psilocybin had a significant decrease in HAMD scores from baseline (22.9, 8.0, and 8.5 at 0, 5, and 8 weeks; $P<.001$), while patients in the control group did not have a change in HAMD scores (22.5, 23.8, and 23.5; $P>.05$). EBP

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Should the presence of chronic kidney disease preclude intravenous contrast administration when considering computed tomography imaging?

EVIDENCE-BASED ANSWER

Patients with chronic kidney disease (CKD) can safely receive low or iso-osmolar intravenous (IV) contrast for computed tomography imaging without an increased risk of contrast induced nephropathy or acute kidney injury within three days of contrast administration (SOR: **B**, meta-analysis of retrospective cohort studies). Patients with CKD stage III or IV do not have an increased risk of contrast-induced acute kidney injury when managed with low osmolar contrast and saline infusion (SOR: **B**, single prospective cohort study).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

In 2019, a meta-analysis of six retrospective cohort studies (N=55,963) evaluated the risk of contrast-induced nephropathy in patients with chronic kidney disease (CKD) who received intravenous (IV) contrasted computed tomography (CT) studies.[1] It evaluated patients with preexisting renal failure who underwent low or iso-osmolar contrast-enhanced CT in comparison with those who received CT without contrast. Patients who did and did not receive contrast ranged from 48 to 59 years old and 53 to 63 years old, respectively. The studies did not evaluate prophylaxis before contrast administration. Study designs included inpatient, emergency, and trauma units in patients with otherwise unspecified CKD. Renal failure was defined as a serum creatinine greater than 1.3 to 1.5 mg/dL or specified according to the National Kidney Foundation by CKD Stage and estimated glomerular filtration rate (eGFR). Contrast-induced nephropathy was defined as an increase in creatinine by 25 to 50% or absolute increase 0.3 to 1.2 mg/dL within three days after contrast administration. Studies without a defined control group were excluded, as were those evaluating contrast use in coronary angiography or other intraarterial contrast administration. The risk of developing contrast-induced nephropathy (CIN) was no different between the groups (6 studies, N=30,775; 7.8% vs 7.5%; odds ratio [OR] 1.1; 95% CI, 0.98–1.2). In patients with CKD stage 4 and CKD stage 5, no difference was noted in rates of CIN compared with controls (4 studies, N=3,518; 14% vs 11%; OR 1.1; 95% CI, 0.86–1.4; I^2=45%). Limitations included a lack of long-term follow-up in most studies. Those that did reported no increase in secondary outcomes such as need for dialysis or renal transplant at six months. Analyses of their eGFR subcategorization showed no significant heterogeneity.

A 2019 prospective cohort study (n=1,541) at a single regional hospital examined the incidence of contrast-induced acute kidney injury after administration of IV contrast for CT imaging.[2] The study included both inpatients and outpatients. These patients (median age of 68 years old and 68% male) had various kidney functions ranging from normal kidney function to CKD stage IV (13% had CKD stage III or IV). CKD was defined by calculated eGFR and staged by the National Kidney Foundation Kidney Disease Improving Global Outcomes criteria. Comorbid conditions stratified included cardiovascular disease, diabetes, and hypertension. Patients with CKD stage III or IV received iso-osmolar contrast material and a prophylactic infusion of normal saline (1.0–1.5 mL/kg/h) before and after IV contrast. Those with normal kidney function and CKD stage I or II received low osmolar contrast material without infusion of normal saline. The primary outcome was the incidence of contrast-induced acute kidney injury, defined as a decrease in eGFR of 25% or more after infusion of contrast. Secondary outcomes included statin and antibiotic therapy and their association with contrast-induced acute kidney injury. Patients with CKD stages III and IV did not have an increased risk of contrast-induced acute kidney injury (OR 0.51; 95% CI, 0.08–1.7). Statin therapy was associated with a decreased in the risk of developing contrast-induced acute kidney injury (OR 0.20; 95% CI, 0.03–0.68), whereas antibiotic therapy was associated with an increased probability of developing contrast-induced acute kidney injury (OR 2.9; 95% CI, 1.2–6.4). EBP

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In women with polycystic ovarian syndrome, does a combination of metformin and oral contraceptive pills work better than either agent alone for the symptom of hirsutism?

EVIDENCE-BASED ANSWER

Yes. The use of metformin and oral contraceptive pills (OCPs) together leads to a greater reduction in hirsutism in adult women with polycystic ovarian syndrome when compared with either intervention on its own. However, gastrointestinal side effects are greater in any treatment group that includes metformin either alone or in combination with an OCP (SOR: **B**, meta-analysis of randomized controlled trial s and results of cohort study).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

In 2019, a meta-analysis of 44 randomized controlled trials (RCTs; N=2,253) compared the effectiveness and safety of metformin and oral contraceptive pills (OCPs) for the treatment of clinical, hormonal, and metabolic features of polycystic ovarian syndrome (PCOS).[1] Patients, 12 to 40 years old, fulfilled the Rotterdam diagnostic criteria for PCOS in most studies. Minimum follow-up was three months. The primary outcomes included hirsutism and adverse events. A trained observer assessed clinical signs of hirsutism with the Ferriman and Gallwey (F-G) scale (total points 1–4, with lower scores being less hirsutism). No difference in F-G scores was noted between the metformin group and the OCP group in adult women with a body mass index (BMI) <25 or >30 kg/m^2. However, metformin was less effective than the OCP in improving hirsutism in adult women with BMI 25 to 30 kg/m^2 (5 RCTs, N=254; MD 1.9; 95% CI, 1.2–2.6). Metformin alone was less effective than metformin plus OCPs at reducing the F-G score (3 RCTs, N=135; MD 1.4; 95% CI, 0.62–2.1; low-quality evidence). Likewise, OCPs were less effective than OCPs plus metformin (6 RCTs, N=228; MD 0.54; 95% CI, 0.2–0.89). In adolescents, no difference in hirsutism scores was noted between metformin and OCPs or between OCPs and OCPs plus metformin. Rates of severe gastrointestinal side effects were higher in the metformin group than in the OCP group (11 RCTs, N=602; Peto odds ratio [OR] 6.4; 95% CI, 3–14; low-quality evidence), but nongastrointestinal severe side effects were less (8 RCTs, N=363; Peto OR 0.2; 95% CI, 0.09–0.44, low-quality evidence). No difference was noted between metformin and metformin plus OCPs for all severe adverse events. Severe gastrointestinal adverse events were less in the OCP group compared with metformin plus the OCP group (5 RCTs, N=228; OR 0.20; 95% CI, 0.06–0.72). No difference was noted between the OCP and metformin plus the OCP for severe other adverse events.

A 2018 RCT (n=90) examined the effectiveness of metformin and OCPs for health-related quality of life, including facial hair, body hair, acne, irregular menses, and weight in women with PCOS.[2] Patients were White women in Denmark, 18–39 years old, BMI <35 kg/m^2, and fulfilled the Rotterdam criteria for PCOS. Patients who were pregnant, had untreated depression, eating disorders, diabetes, or contraindications to metformin or OCP were excluded. The study included 40 women with regular menstrual cycles, normal ovaries, and hirsutism as a baseline control. The patients were randomized into three different medical intervention groups, metformin 2,000 mg/day, oral contraceptive pill desogestrel 150 mg with ethinyl estradiol 30 mcg/day), and metformin plus the OCP for 12 months. Researchers assessed the primary clinical outcomes of facial hair, body hair, acne, menstrual irregularities, weight, and PCOS using a 0- to 100-mm visual analog scale, where higher scores indicated more severe discomfort. A small decrease in facial hair growth was noted with 12 months of treatment with OCP alone (MD –1.2; 95% CI, –2.9 to –0.2) or in combination with metformin (MD –2.7; 95% CI, –5.2 to –1.0), but no difference with metformin only. Both the OCP and the OCP plus metformin groups were superior to treatment with metformin alone (–1.2 vs 0; $P<.05$ and –2.7 vs 0; $P<.05$). No difference in body hair was noted with any of the treatments. Although a statistical difference was noted between the groups, this may not have actual clinical significance given the small point difference between the groups on the 100-point scale that was used. Limitations included a high dropout rate of 28%, with 7.8% of those reporting side effects. A pharmaceutical company supplied the study medications. EBP

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Are probiotics effective at improving symptoms in adults with atopic dermatitis?

EVIDENCE-BASED ANSWER

Oral probiotics seem to improve symptoms of atopic dermatitis by 16% to 35%, as measured by SCORAD score (SOR: **A**, meta-analysis of 6 randomized controlled trials [RCTs] and a single RCT). Topical probiotic ointment may not be any more effective than placebo ointment (SOR: **C**, small RCT).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2022 meta-analysis of six randomized controlled trials (RCTs; N=241) examined the effectiveness of probiotics in adults with atopic dermatitis.[1] The intervention group (n=128) included patients ranging from 14 to 65 years old who received oral doses of 2×10^{10} CFU *Lactobacillus plantarum* daily, 1×10^{9} CFU *Lactobacillus salivarius* twice daily, 1×10^{9} CFU/g *Lactobacillus salivarius*, and *Bifidobacterium breve* twice daily, 20.7 mg/day *Lactobacillus acidophilus*, 2×10^{11} *Lactobacillus paracasei* daily, or 6×10^{9} CFU *Bifidobacterium animalis* daily, mixed with various inert compounds. The control group (n=113) received oral doses of the corresponding inert compounds. Study time frames ranged from eight to 16 weeks. The outcomes of itch and skin severity were assessed at various time points across each study, with quality of life measured at the end of therapy. Atopic dermatitis severity was measured with the validated SCORAD score, Dermatology Life Quality Index, or the Skindex-16 and Skindex-29. No information was provided on assessment of skin severity and itch severity. Probiotics improved overall atopic dermatitis severity and quality of life versus the control group (see **TABLE 1**). Limitations included small total numbers of patients, no available data for side effects of probiotics, variable follow-up periods, and heterogeneity of strains of probiotics used.

A 2021 RCT (n=80) examined the effectiveness of oral probiotic supplements in treating symptoms of atopic dermatitis.[2] Adults, 18 to 50 years old, with mild-to-moderate atopic dermatitis based on a SCORAD index score of 15 to 25, were divided into an intervention group and a control group. Researchers excluded patients who used systemic corticosteroids or antihistamines within the last three months or probiotics within the last six months. The intervention group (n=40, 83%

TABLE 1. Outcomes for the probiotic group versus the control group in six RCTS in adults with atopic dermatitis[1]

	No. of Studies	No. of Patients	Mean Difference (95% CI)
SCORAD score	3	114	**–7.1 (–7.3 to –6.9)**
Skindex	2	68	**–7.7 (–14.1 to –1.3)**
DLQI	2	84	–0.96 (–2.8 to 0.89)
Itch Severity	2	77	–0.17 (–0.6 to 0.26)
Skin Severity	2	77	–0.19 (–0.67 to 0.30)

Statistically significant outcomes are in bold font. Skindex (a quality of life measure), two versions but both range 0 to 300. DLQI, Dermatology Life Quality Index (range 0–13); MD, mean difference; SCORAD, SCORing Atopic Dermatitis (range 0–103).

TABLE 2. Outcomes for probiotic mix versus placebo after 84 days of treatment in an RCT of 80 patients[2]

	Probiotic		Placebo		
	Baseline	Day 84	Baseline	Day 84	*P*
SCORAD score	20.9	14.8*	19.7	17.6	<.001
Skin smoothness (% improved subjects)	—	77.5	—	30.0	<.01
Skin moisturization (% variation)	—	28.3	—	9.9	<.001
Transepidermal water loss (% variation)	—	–15.0	—	–2.8	<.001

SCORAD, SCORing Atopic Dermatitis (range 0–103).

females) received a once-daily oral capsule containing a mixture of three lactobacilli strains combined with corn starch and vegetable magnesium stearate, whereas the control group (n=40, 87% females) took capsules of vegetable magnesium stearate and corn starch. After a one-month wash-out period, both groups continued the product through day 56. Dermatologic evaluations were conducted at baseline (day 0) and at days 28, 56, and 84. Primary outcomes included the SCORAD score, skin smoothness and moisturization, and transepidermal water loss. Skin softness was clinically scored across four levels, not smooth (1) to clearly smooth (4). Skin moisturization was assessed using corneometry that measures the dielectric content of skin, whereas transepidermal water loss was determined using a Tewameter and measuring the integrity of the skin protective barrier. Oral probiotics improved symptoms of atopic dermatitis including skin smoothness, transepidermal water loss, and SCORAD score (see **TABLE 2**). No adverse events were reported during the study. Lack of generalizability to males is a study limitation.

A 2020 randomized, double-blind controlled study (n=34) examined the effectiveness of topical probiotic ointment on atopic dermatitis.[3] Adults (19–66 years old) with atopic dermatitis and a SCORAD index >25 participated in a two-week run-in period before randomization to the intervention or control groups. Researchers excluded patients any chronic medical conditions or who took any immunomodulatory medication. The intervention group (n=17, 100% female) used an ointment containing *Lactobacillus reuteri*, shea butter, and canola oil, whereas the control group used an ointment of shea butter and canola oil (n=17, 88% female). Patients applied the ointment to affected areas twice a day for eight weeks. Symptoms were assessed by a dermatologist using SCORAD index and local SCORAD at baseline (day 0), day 28, and day 56. SCORAD index is the sum of different factors (area of involvement, intensity of lesions, and subjective symptoms), whereas local SCORAD only looks at intensity. A nonstatistical improvement in SCORAD index and local SCORAD score was noted between probiotic ointment group and the control group, although the probiotic ointment showed more improvement than the control. No adverse or serious adverse events were reported. A majority of female participants limited generalizability of the study. EBP

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In hospitalized patients, does the use of earplugs at night decrease the incidence of hospital-acquired delirium?

EVIDENCE-BASED ANSWER

The use of earplugs may reduce the incidence of delirium by 50% and improve subjective sleep quality in hospitalized patients (SOR: **C**, systematic review with significant heterogeneity, and 2 randomized controlled trials with inconsistent findings).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2018 systematic review of 19 randomized controlled trials (RCTs; N=1,379) compared the use of earplugs and eye masks with standard care on the quality of sleep in adult patients admitted to the intensive care unit (ICU).[1] Patients assigned to the treatment group received earplugs, eye masks, or both, individually or in combination with relaxing music, whereas those assigned to the control group received the standard of care without nonpharmacologic interventions. Sleep quality was evaluated with objective (polysomnography, hormone levels) or subjective measures (original questionnaires, Richards Campbell Sleep Questionnaire [RCSQ], Pittsburgh Sleep Quality Index, and Verran and Snyder-Halpern Sleep Scale). The RCSQ assesses perceived sleep quality through a five-item questionnaire over six domains (depth, latency, awakenings, proportion of time awake, quality of sleep, noise perception; each question scored 0–100, with higher scores indicating better sleep; total score is the average of individual questions). Of the 18 trials that subjectively measured quality of sleep, 17 revealed significant improvement with the use of earplugs and eye masks. In one study, earplug and eye mask use resulted in a reduction in mean rapid eye movement (REM) latency (106.7 vs 147.8 minutes, $P=.02$) as well as increased percentage of REM sleep (9.9% vs 14.9%, $P=.04$). In two of the three studies using the RCSQ to subjectively assess sleep quality, earplug and eye mask use resulted in an improvement in all five questions. The third study did not show improvement. A 2012 RCT (n=136) showed a reduction of delirium with earplug and eye mask use by 53% (hazard ratio [HR] 0.47; 95% CI, 0.27–0.87). A 2012 observational study with a predesign and a postdesign (n=300) showed a difference of 48% in incidence of delirium (odds ratio [OR] 1.6; 95% CI, 1.0–2.6). Given that the quality of sleep was assessed using various methodologies, heterogeneity was a significant limitation and did not allow a full meta-analysis.

A 2021 RCT (n=100) examined the effects of earplugs and eye masks on the quality of sleep, patient satisfaction, reduction in nurse demands, and in the incidence of delirium in patients after major abdominal surgery.[2] The study included patients over 21 years old with a Glasgow Coma Scale ≥10 postoperatively. Patients were excluded if they had known hearing impairment, dementia, confusion, delirium, or preexisting tracheostomy or who returned to the ward after surgery later than 10:00 PM. Patients were randomly allocated into routine care (no earplugs and eye masks, n=48) or intervention (given earplugs and eye masks, n=45). The primary outcome was sleep quality on postop days 1 to 3 measured by the RCSQ. Scores for days 1, 2, and 3 were 60, 56, and 62 for the intervention group and 64, 60 and 66 for the control group ($P=.310$), respectively. No significant difference regarding patents' satisfaction was noted. The use of earplugs and eye masks did not reduce the frequency of a nurse attending the patient (OR 1.1; 95% CI, 0.61–1.9) or the frequency at which nursing was conducted (OR 1.33; 95% CI, 0.62–2.9). No difference in the incidence of delirium was found over the three days postop. Limitations included difficulty ensuring patient compliance with intervention, retrospectively collected data that may have introduced recall bias, and differences in recovery from different procedures.

A 2021 prospective RCT (n=77) conducted in the surgical ICU, examined the impact of earplugs and eye masks on sleep quality in postoperative surgical ICU patients.[3] Patients were adult females admitted to the surgical ICU requiring hourly postoperative assessments. Exclusion criteria included pregnancy, current incarceration, and diagnosis of sleep apnea, insomnia, or other sleep disturbance. Patients were randomly assigned in a 1:1 ratio to an intervention group that received standard

postoperative care plus earplugs and eye masks or a control group that received only standard postoperative care. All patients completed the RCSQ after every night in the ICU and a modified version of the Family Satisfaction in the ICU (FS-ICU) survey on ICU discharge. The Confusion Assessment Method for the ICU (CAM-ICU) was used to assess for delirium nightly. Primary outcome was the difference in RCSQ total score after the first ICU night between the control and intervention groups. Secondary outcome measures included differences in overall modified FS-ICU scores and CAM-ICU scores between the two groups. The average RCSQ score was significantly higher in the intervention group compared with the control group (65 vs 47, $P=.0007$). No between-group difference in the rate of delirium was found because no patients in either group had positive CAM-ICU scores. No significant differences between groups for any of the modified FS-ICU survey questions were found. No adverse events were reported. Limitations included the small study size, strict exclusion criteria, a homogeneous patient population, and potential bias had nurses modified their behavior when encountering patients wearing earplugs and eye masks. EBP

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The authors declare no conflicts of interest.

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Do naloxone access laws decrease opioid-related deaths?

EVIDENCE-BASED ANSWER

Naloxone access laws including prescriptions for naloxone may help reduce opioid-related deaths (SOR: **B**, inconsistent cohort studies). There may also be a decrease in opioid-related deaths after implementation of overdose education and nasal naloxone distribution (SOR: **B**, single cohort study).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A systematic review analyzing 11 studies compared the implementation of naloxone access laws in the United States with opioid-related mortality, opioid-related emergency department (ED) visits, and naloxone distribution.[1] The review included trials published after 2018 and assessed at least one opioid- or naloxone-related outcome in adult opioid users. Five studies discussed naloxone access laws (NALs) in association with naloxone access. Generally, an increase in naloxone prescriptions was noted in states with some form of NAL (incidence rate ratio 1.40 vs 7.8). Six studies analyzed the association of NALs with opioid overdose. One study described a 23% reduction in overdoses related to prescriber immunity provisions but no significant associations with other NAL components (incidence rate ratio 0.66 vs 1.27). However, other related studies found no difference or an increase in opioid-related deaths after the adoption of NALs. Finally, three studies discussed the association between NALs with opioid-related ED visits. Overall, studies found an increase in opioid-related ED visits in states that implemented NALs (95% CI, 1.07–1.2). Of note, studies did not show increased harm with nonprescriptive naloxone distribution. The authors concluded that insufficient evidence exist to prove that NALs are beneficial although some positive effects are seen. Limitations included variability state to state in specific components of NALs and specific opioids that are more prevalent in certain locations—areas with a higher incidence of heroin and fentanyl had a higher death rate.

An observational study published in 2018 assessed the relationship between laws related to opioid overdose reversal—namely NAL and overdose Good Samaritan laws—and opioid overdose mortality as well as nonmedical opioid use.[2] The existence of NAL (n=28 states) and overdose Good Samaritan laws (n=21 states) from all 50 states and the District of Colombia were evaluated from 2000 to 2014. Mortality population included all patients in these locations, whereas the population for the opioid-use outcomes included noninstitutionalized individuals 15 years old and older. After enacting an NAL, states had 14% lower incidence of opioid-overdose deaths (P=.033). After enacting an overdose Good Samaritan law, states had a 15% lower incidence of opioid-overdose deaths (P=.050). No statistically significant increases were noted in the prevalence of nonmedical opioid use. Mismeasurement of classification of opioid overdoses by coroners and medical examiners may have affected precision of mortality estimates.

A study from 2013 included an interrupted time series analysis of opioid-related overdose death and acute care hospital utilization rates from 2002 to 2009 in Massachusetts.[3] It compared community-year strata with high and low rates of overdose education and nasal naloxone distribution (OEND) implementation to those with no implementation. This study included 19 Massachusetts communities with at least five fatal opioid overdoses in each of the years 2004 to 2006. Implementation of OEND was associated with lower rates of opioid-related deaths from overdose with adjusted rate ratio (aRR) 0.73 (95% CI, 0.57–0.91) for low implementation groups with 1 to 100 enrollees per 100,000 and aRR 0.54 (95% CI, 0.39–0.76) for high implementation groups with >100 enrollees per 100,000. This study had several limitations such as the true population of opioid users in each community was not known and opioid overdose fatalities may not have been classified as such, but the authors attempted to account for this in their analysis. EBP

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