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EVIDENCE-BASED PRACTICE

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EVIDENCE-BASED PRACTICE
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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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SPOTLIGHT ON PHARMACY

EVIDENCE-BASED PRACTICE

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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

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DISCLOSURE

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Is montelukast effective for treating patients with chronic urticaria?

EVIDENCE-BASED ANSWER

Montelukast was superior to placebo, inferior to desloratadine and cetirizine, and enhanced the effect of nonsedating antihistamines when combined with them (SOR: **B**, systematic review of heterogenous randomized controlled trials [RCTs]). For patients who have failed cetirizine alone, adding montelukast has greater therapeutic effect than adding ranitidine (SOR: **B**, small RCT).

DOI 10.1097/EBP.0000000000001208

In 2014, a systematic review of six randomized trials compared the efficacy of montelukast and antihistamines (cetirizine, desloratadine, and fexofenadine) versus montelukast alone.[1] These six studies included 342 patients with ages ranging from 18 to 69 years. The usual duration was about six weeks. The primary outcomes were the number of wheals, total urticarial symptom score (TSS), urticarial activity score, weekly antihistamine count, visual analog score, pruritus, quality of life score, and interference with daily activities and sleep (see **TABLE 1**). One study showed that adding montelukast to cetirizine or desloratadine had a greater therapeutic effect in patients with chronic urticaria than adding montelukast alone. Montelukast monotherapy was superior to the placebo in three of the studies, and only one study showed that montelukast alone improved the total symptom score. However, in that study, fexofenadine was used instead of the other antihistamines. No significant adverse effects were observed between the groups. Limitations of the study included variation in outcome measures between the studies because they used different types of scores, and many of the studies were not sufficiently powered. Additionally, the heterogeneity between the studies did not allow for pooling of the cumulative data.

TABLE 1. Summary of effects of montelukast in six studies[1]

Outcome measures	Study first author	Montelukast vs placebo	Montelukast+antihistamine vs antihistamine	Montelukast vs antihistamine
Pruritus	Di Lorenzo			Favors desloratadine
	Nettis		Favors montelukast	
	Godse			Favors cetirizine
No. of wheals	Di Lorenzo	Favors montelukast		Favors desloratadine
	Nettis		Favors montelukast	
Interference with sleep	Di Lorenzo			Favors desloratadine
Interference with daily activities	Di Lorenzo	Favors montelukast		
Quality of life score	Nettis		Favors montelukast	
TSS	Di Lorenzo	Favors montelukast		Favors desloratadine
	Nettis			Favors montelukast (vs. fexofenadine)
Size of wheals	Erbagci	Favors montelukast		
	Agcaoili	Favors montelukast		

TABLE 2. Weekly summed urticaria activity scores (UAS) among study participants[2]

Week	Mean Score montelukast+cetirizine	Mean Score ranitidine+cetirizine	P
1	18.8	27.6	.0001
2	10.3	19.4	.0001
3	4.9	13.9	.0001
4	1.9	8.2	.0001
Total	35.9	69.2	.0001

The mean score was calculated by the sum of daily calculated UAS score (0–six points) for one week total (range 0–42 points), with a higher score indicating more severe symptoms.

In 2018, a prospective, randomized, open-label study compared the efficacy of combined therapy of montelukast and cetirizine versus combined therapy with ranitidine and cetirizine in patients with chronic urticaria. [2] One hundred patients 18 to 60 years were enrolled; of whom, 93 completed the study (62 women and 31 men). Inclusion criteria consisted of patients who did not respond to two weeks of treatment with cetirizine, urticaria of greater than six weeks duration, no treatment with steroids and other immunosuppressant for urticaria or other diseases, and no urticaria associated with other skin disorders like eczema. The duration of study was six weeks, four weeks of therapy with two weeks of follow-up. The primary outcome was the urticaria activity score (UAS), a patient-reported outcome that assesses itch severity scale (0=none, 1=mild, 2=moderate, 3=severe) and number of wheals (0=none, 1=0–20 wheals/24 h, 2=20–50 wheals/24 h, 3=≥50 wheals/24 h). Daily scores were summed at the end of every week (range, 0–42) for the period of four weeks. UAS scores decreased in both groups, but a comparatively greater decrease in UAS was seen in cotherapy with montelukast than in cotherapy with ranitidine (see **TABLE 2**). No significant difference was observed in biomarkers or adverse effects between the two groups. Secondary outcomes (hemoglobin, total leukocyte count, eosinophil count, ESR, liver profile, and other biomarkers), as well as adverse effects (sedation, dizziness, headache), were also examined but resulted in no significant differences between the two groups. EBP

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The authors declare no conflicts of interest.

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2. Dinesh S. *Efficacy of Montelukast and Ranitidine as an Add on Therapy for Chronic Urticaria*: SciDoc Publishers: International Journal of Clinical Pharmacology & Toxicology, 2018. https://scidoc.org/IJCPT-2167-910X-07-102.php. [STEP 2]

Expert opinion

The evidence-based medicine community is never surprised when experts turn out to be wrong. This is because experts are as subject to bias and error as everyone else. Take, for example, the chestnut that humans have a poorly developed sense of smell. That notion gradually became "common knowledge" over a period of about 100 years.[1] It is a case study in why experts should be questioned and hypotheses tested.

French neuroanatomist Pierre Paul Broca (1824–1880) seems to have started it. Fascinated with frontal and olfactory lobe neuroanatomy across species, he classified mammals as either "osmatic" (where smells drove behavior) or "non-osmatic" (where smells did not obviously drive behaviors). He placed humans and the other primates in the non-osmatic category because we choose (with our big frontal lobes) whether to react to olfactory stimuli or not.

Later, English anatomist Sir William Turner (1832–1916), perhaps not quite understanding Broca's French, subdivided Broca's non-osmotics into "anosmotics" (whales and dolphins) and "microsmotics," (the primates again) stating—without evidence—that our sense of smell was "rather feeble." Taking the misunderstanding a step further, by 1924 Charles Judson Herrick (1868–1960) stated in his book *Neurological Foundations of Animal Behavior* that human olfactory bulbs were nearly "vestigial" and that other animals' keen sense of smell was "beyond our comprehension."

But wait! According to olfactory physiologist John P. McGann—a man who spent his career testing these hypotheses—human olfaction is actually quite good. While we have fewer types of smell receptor proteins than other animals, we have the same number of olfactory neurons, more complex higher level processing, and the ability to smell almost all volatile organic compounds. Humans noses, however, are "tuned by evolution." We are best at picking up key smells important to the species. It didn't surprise me to learn from McGann that we are particularly good at picking up the smell of bananas.

Experts may have humble feet of clay, but those aquiline noses they sometimes look down are better sense organs than some of them ever expected.

DOI 10.1097/EBP.0000000000001493

Reference

1. McGann FP. Poor human olfaction is a 19th-centuty myth. *Science*. 2017;356(6338). pii: eaam7263.

Zoledronate reduces risk of fractures in women with osteopenia

Reid IR, Horne AM, Mihov B, et al. Fracture Prevention with Zoledronate in Older Women with Osteopenia. *N Engl J Med*. 2018 Dec 20; 379(25):2407–2416.

DOI 10.1097/EBP.0000000000000597

This is a double-blind placebo-controlled trial involving 2,000 New Zealand women with osteopenia (T-score of –1.0 to –2.5 at total hip or either femoral neck) randomized to either intravenous zoledronate 5 mg or intravenous normal saline placebo given every 18 months over a six-year study. The primary outcome was time to first fragility fracture with secondary end points being symptomatic fractures, vertebral fractures, change in height, and mortality. Mean patient age was 71 years old, and more than 94% were of European descent. Women with one T score of less than –2.5 were not excluded, as long as another site met osteopenia criteria. At the conclusion of the study, the hazard ratio (HR) for a fragility fracture with zoledronate was 0.63 (95% CI, 0.59–0.79) with the number needed to treat [NNT] to prevent the occurrence of a fragility fracture in one woman being 15. The secondary end point of symptomatic fracture had an HR with zoledronate of 0.73 (95% CI, 0.60–0.90), and the NNT to prevent a symptomatic fracture in one woman was 20. For nonvertebral fragility fractures zoledronate was associated with an HR of 0.66 (95% CI, 0.51–0.85,) and the NNT to prevent a nonvertebral fragility fracture was 22.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	Yes	Clinically meaningful	Yes

Bottom line: Four doses of zolendronate 5 mg over six years are associated with a decrease in fragility fractures in postmenopausal women with osteopenia. This trial addresses a lack of data about prevention of fractures in osteopenic women.

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The authors declare no conflicts of interest.

Clinical cure of group A streptococcal pharyngotonsillitis with a five-day treatment of penicillin V

Skoog Ståhlgren G, Tyrstrup M, Edlund C, et al. Penicillin V four times daily for five days versus three times daily for 10 days in patients with pharyngotonsillitis caused by group A streptococci: randomised controlled, open label, non-inferiority study. *BMJ*. 2019; 367:l5337.

DOI 10.1097/EBP.0000000000001178

Study summary

This open-label, randomized controlled, noninferiority study compared two dosing regimens of penicillin (Pen) V with treat group A streptococcal pharyngotonsillitis. The standard treatment (recommended in European and American guidelines)[1,2] of 10 days of Pen V 1,000 mg three times a day (total 30 g) was compared with a five-day treatment regimen of Pen V 800 mg four times a day (total 16 g). Dosage adjustments for weight were made for children up to 40 kg with those weighing 10 to 20 kg receiving 250 mg per dose and those weighing 20 to 40 kg receiving 500 mg per dose regardless of treatment arm. The main outcome was clinical cure 5 to 7 days after completion of treatment. This was defined as "complete recovery without major residual symptoms or clinical findings of pharyngotonsillitis or symptomatic relapse." The noninferiority margin was prespecified to 10%. Secondary outcomes were bacterial eradication, time to relief of symptoms, frequency of relapse, complications and new tonsillitis, and patterns of adverse events. Patients aged six years and older were recruited from 17 primary health care centers in Sweden between September 2015 and February 2018. Participants who met the inclusion

criteria had a positive rapid antigen test for group A Strep and met three or four Centor criteria. Centor Criteria for this study included "fever >38.5 C, tender lymph nodes, coatings of the tonsils (for children inflamed tonsils), and absence of cough." Clinical cure between the five-day and 10-day groups proved similar in both the per-protocol population (89.6% and 93.3%, respectively; difference, –3.7; 95% CI, –9.7 to 2.2) and the modified intention-to-treat population (89.6% and 93.8%, respectively; difference, –4.2; 95% CI, –9.9 to 1.5), thus proving noninferiority.

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 "PenV," "Penicillin," "group A streptococcus," "pharyngitis," "pharyngotonsillitis," and "duration of therapy" 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	No	Implementable	Yes
Change in practice	No	Clinically meaningful	No

Bottom line: In patients older than six years who present with a positive rapid test for group A Strep and three or four Centor criteria, treatment with five days of Penicillin V four times a day proves noninferior to 10 days of treatment three times a day to achieve a clinical cure. The validity and clinical utility of this finding are attenuated because the "clinical cure dates" were many days past when most patients would experience symptom resolution without antibiotic treatment. The effect (if any) on cardiac complications could not be assessed.

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Send low-risk syncopal patients home from ED with new risk stratification tool

Thiruganasambandamoorthy V, Sivilotti MLA, Le Sage N, et al. Multicenter emergency department validation of the Canadian syncope risk score. *JAMA Intern Med*. 2020; 180(5):737-744.

DOI 10.1097/EBP.0000000000001203

This prospective cohort validation study evaluated if the Canadian Syncope Risk Score (CSRS) can accurately risk stratify patients who present to the emergency department (ED) within 24 hours of a syncopal event (N=3,819 consecutive patients 16 years old or older). Components of the CSRS include predisposition to vasovagal symptoms (–2 points), history of heart disease (1), systolic pressure <90 or <180 (1), elevated troponin level (2), abnormal QRS axis (1), QRS duration >130 ms (1), corrected QT interval >480 ms (2), diagnosis of vasovagal syncope in the ED (–2), and diagnosis of cardiac syncope in the ED (2). Blinded assessors reviewed medical records to identify serious adverse effects including arrhythmia, intervention to treat arrhythmia, death because of unknown cause, or nonarrhythmic serious conditions such as myocardial infarction within 30 days of the initial presentation. Loss to follow-up was 3.6%. An adverse event was experienced in 3.6% of patients. In the very low-risk group (score of –3 or –2), 0.2% experienced adverse events (0 deaths); in the low-risk group (score –1 or 0), adverse events occurred in 0.7% (0 deaths); and in medium risk group (score 1–3), 8% experienced adverse events (1 death). In the high-risk group (score 4 or 5), 19% experienced adverse events (5 deaths); in the very high-risk group (score 6–11), 51% experienced adverse events (7 deaths). Overall, the sensitivity of the tool at a threshold score of –1

was 98% (95% CI, 94–99.6) and specificity was 44% (95% CI, 43–46).

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, Dyna Med, ACC/AHA Guidelines with the terms [syncope risk stratification and emergency department] 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	Yes	Clinically meaningful	Yes

Bottom line: The Canadian Syncope Risk Score has been validated to risk stratify patients presenting to the emergency department within 24 hours of syncope into very low, low, medium, high, and very high categories. Applying these criteria, providers can safely send home very low- and low-risk patients from the emergency department because of the low probability of serious events within the next 30 days.

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The authors declare no conflicts of interest.

Teaching your bladder to behave

Burgio KL, Kraus SR, Johnson TM II, et al. Effectiveness of combined behavioral and drug therapy for overactive bladder symptoms in men: A randomized clinical trial. *JAMA Intern Med*. 2020; 180(3):411–419.

DOI 10.1097/EBP.0000000000001198

This two-stage unblinded randomized clinical trial compared behavioral treatment, medication therapy, and a combined approach for treatment of overactive bladder (OAB) symptoms in adult community dwelling men (N=204). Patients must record at least nine daily voids pretrial and were stratified based on the presence of urge incontinence and number of voids. Behavioral therapy included pelvic floor muscle training with urge suppression strategies and delayed voiding. Medication therapy included sustained-release tolterodine 4 mg daily and tamsulosin 0.4 mg every evening. The third group combined the two strategies. After six weeks, all patients moved to combination therapy for six more weeks. Study measurements were collected at baseline, six and 12 weeks. In the first six weeks of the trial, 21 men (10%) discontinued treatment, with six lost to follow-up, 12 unable to attend visits, and two unable to tolerate the study drug. No difference was noted in drop out among groups.

The primary outcome was change in number of daily voids with secondary outcomes of urgency, incontinence, and episodes of nocturia. At six weeks, patients in the combined group reported lower voiding frequencies compared with the drug therapy group (change of –3.6 vs –1.5 voids per day; $P<.001$) but not compared with the behavioral therapy group (change of –3.6 vs –2.9 voids per day; $P=.19$). The primary outcome decreased in all initial assigned treatment groups at 12 weeks compared with baseline (behavioral therapy –3.7 voids per day, $P<.001$; medication therapy –3.2 voids per day, $P<.001$; and combination therapy –3.8 voids per day, $P<.001$). No statistical difference was noted in the primary outcome among treatment groups at 12 weeks. Weekly incontinence episodes decreased 78.8% in the combined therapy group, 52.9% in the behavioral group, and 52.7% in the drug therapy group. No difference was noted in patient satisfaction by treatment group. The most common side effects of dry mouth and constipation occurred with use of medication therapy alone and in combination. These results are limited by a short follow-up period.

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 and UpToDate with the terms overactive bladder in men to find additional literature to place this research into the context of current clinical practice.

Bottom line: Combining behavioral and drug therapy yielded greater improvement in overactive bladder

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

symptoms compared with drug therapy alone but not behavioral therapy alone at six weeks. By 12 weeks, no difference was noted in urinary frequency among treatment strategies. This enforces findings in prior literature that behavioral therapy is a reasonable starting point for management of OAB or is useful as an adjunct to medication therapy.

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The authors declare no conflicts of interest.

No rest for the weary

The prevalence of sleep disturbances among physicians and nurses facing the COVID-19 patients: a systematic review and meta-analysis

Salari N, Khazaie H, Hosseinian-Far A, et al. The prevalence of sleep disturbances among physicians and nurses facing the COVID-19 patients: a systematic review and meta-analysis. *Globalization & Health*. 2020; *16*(1):N.PAG. doi:10.1186/s12992-020-00620-0. DOI 10.1097/EBP.0000000000001383

KEY TAKEAWAY: 35% of nurses and 42% of physicians working among COVID-19 patients experience sleep disturbances.

STUDY DESIGN: Meta-analysis and systematic review of seven cross-sectional studies.

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: As the pandemic continues across the globe, health care workers are experiencing mental health challenges from caring for patients with SARS-CoV-2.

PATIENTS: Physicians and nurses working in hospitals
INTERVENTION: Sleep surveys of doctors and nurses treating patients with COVID-19
CONTROL: None
OUTCOME: Prevalence of sleep disturbances

METHODS BRIEF DESCRIPTION:

- Seven articles were used for the study after being assessed for methodological quality using the STROBE checklist (title, problem, objectives, study type, sample size, variables and procedures, methods, statistical analysis, and findings).
- A cutoff score of 16 of 32 was used to be considered as medium- or high-quality articles.
- Three studies used the Sleep Disturbances Severity Index with possible scores ranging from 0 to 28, using a cutoff of >8, indicating sleep disturbances.
- Three studies used the Pittsburgh Sleep Quality Index with possible scores ranging from 0 to 21, using a cutoff score of >7, indicating sleep disturbances.
- One study used the Athens Sleep Disturbances Scale with possible scores ranging from 0 to 15, using a cutoff score of >6, indicating sleep disturbances.

INTERVENTION (# IN THE GROUP): 3,745 nurses and 2,123 physicians

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW UP PERIOD: December 2019 to June 26, 2020

RESULTS:

- Prevalence of nurses working with COVID-19 patients having sleep disturbances: 35% (6 trials, N=3,745; 95% CI, 25–46; I^2=97%).
- Prevalence of physicians working with COVID-19 patients having sleep disturbances: 42% (6 trials, N=2,123; 95% CI, 29–57; I^2=97%).
- Older physicians experienced a higher prevalence of sleep disturbances compared with younger physicians ($P<.05$; data presented as a meta-regression chart).
- Older nurses experienced a decreased prevalence of sleep disturbances compared with younger nurses ($P<.05$; data presented as a meta-regression chart).

LIMITATIONS:

- Unable to evaluate confounders or sleep disturbances over time due to the cross-sectional study design.
- Not globally representative as six of the seven studies were conducted in China.
- Studies in the pre-print stage were not included.
- Only included studies that subcategorized results under nurses or physicians specifically.
- All data were self-reported.

EBP

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Is HCQ effective in the in-patient treatment of COVID-19?

Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19

Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *International Journal of Infectious Diseases*. 2020; 97: 396–403. DOI 10.1097/EBP.0000000000001251

KEY TAKEAWAY: Treatment of polymerase chain reaction-confirmed, hospitalized COVID-19 patients with hydroxychloroquine (HCQ) or a combination of HCQ plus azithromycin (AZM) is associated with lower in-hospital mortality compared with patients receiving neither drug.

STUDY DESIGN: Multicenter, comparative, retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: COVID-19 is a disease caused by a novel virus. At the time of this study, there was no vaccine or consensus on treatment. It is thought that the pathophysiology of COVID-19 involves a hyperimmune response, and early treatment is paramount in mitigating this response. Various approaches were being considered and studied.

PATIENTS: Adult patients hospitalized with polymerase chain reaction (PCR)-confirmed COVID-19 in a six-hospital health system in southeast Michigan
INTERVENTION: HCQ, AZM or a combination of HCQ and AZM
CONTROL: No HCQ, AZM, or a combination of HCQ and AZM

OUTCOME: In-hospital mortality

METHODS BRIEF DESCRIPTION: The charts of 2,541 hospitalized patients in the Henry Ford Health System (SE Michigan) between March 10, 2020, and May 2, 2020, with PCR-confirmed COVID-19, older than 18 years and with a median age of 64 years, were reviewed to see if they were given HCQ (400 mg twice on day 1, then 200 mg twice daily on days 2–5), AZM (500 mg once on day 1, then 250 mg once daily for 4 days), HCQ and AZM, or neither drug. The mortality rates of each of these groups were calculated. Nearly all (91%) patients who received HCQ started treatment within 48 hours of admission.

INTERVENTION (# IN THE GROUP): 2,132

COMPARISON (# IN THE GROUP): 409

FOLLOW-UP PERIOD: 28 days

RESULTS:
Compared with those receiving neither medication, patients receiving either HCQ alone or HCQ+AZM had a decreased in-hospital mortality rate, controlling for pre-existing conditions and clinical disease severity. Patients receiving AZM alone did not have a lower in-hospital mortality rate.
Mortality rates by intervention:
- HCQ 14% (hazard ratio [HR] 0.34; 95% CI, 0.25–0.46)
- AZM 22% (HR 1.1; 95% CI, 0.68–1.6)
- HCQ+AZM 20% (HR 0.29; 95% CI, 0.22-0.40)
- Neither medication 26%

Mortality with HC alone was also lower with propensity matching (HR 0.49; 95% CI, 0.29–0.83).

LIMITATIONS:
This study was a retrospective, nonblinded cohort trial. It did not indicate how long patients were symptomatic prior to hospitalization. Furthermore, only the initial visit was included for patients with multiple admissions. EBP

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Should clinicians recommend weight loss interventions for patients with nonalcoholic fatty liver disease?

Association of weight loss interventions with changes in biomarkers of nonalcoholic fatty liver disease: a systemic review and meta-analysis

Koutoukidis D, Astbury NM, Tudor KE, et al. Association of weight loss interventions with changes in biomarkers of NAFLD. *JAMA Intern Med*. 2019; 179(9): 1262–1271. DOI 10.1097/EBP.0000000000001150

KEY TAKEAWAY: In patients with nonalcoholic fatty liver disease (NAFLD), weight loss improved biomarkers of liver disease in the short and medium term. Limited long-term follow-up was observed.

STUDY DESIGN: Systematic review and meta-analysis of 22 randomized controlled trials (RCTs); N=2,588

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Guidelines recommend physicians counsel lifestyle modification for NAFLD or nonalcoholic steatohepatitis (NASH). These recommendations are based on observational data, associations between weight loss, and improvements in NAFLD remain unclear

PATIENTS: Adults with NAFLD or NASH
INTERVENTION: (1) Behavioral weight loss programs (BWLPs) including energy-restricted diets and an exercise component or (2) pharmacotherapy (orlistat, liraglutide, or sibutramine hydrochloride) or (3) surgical gastric balloon
CONTROL: Usual care, low-intensity BWLP, or placebo
OUTCOME: Alanine aminotransferase (ALT) and weight, insulin resistance index, steatosis examined by ultrasound, magnetic resonance imaging, or histology, also aspartate aminotransferase (AST), alkaline phosphatas, gamma-glutamyltransferase, Enhanced Liver Fibrosis score, NAFLD fibrosis score, and fatty liver index

METHODS BRIEF DESCRIPTION: Comprehensive systematic review and meta-analysis of RCTs involving NAFLD or NASH on BWLPs (with or without pharmacotherapy) or surgical gastric balloon placement compared with usual care, low-intensity BWLPs, or placebo and reported weight loss and biomarker outcomes.

INTERVENTION (# IN THE GROUP): 1,496
COMPARISON (# IN THE GROUP): 1,062

FOLLOW-UP PERIOD: Range 3 to 8 months (mean 6 months); one RCT with follow-up of five years

RESULTS:
- Intensive weight loss interventions (IWLIs) were significantly more effective than no or lower-intensity weight loss interventions (22 trials; N=2,558; mean difference [MD] −3.6 kg; 95% CI, −5.1 to −2.1).
- IWLIs significantly reduced ALT, but of likely small clinical significance (25 trials, N=2,558; MD −9.81 U/L; 95% CI, −13.1 to −6.5).
- IWLIs were associated with a significant reduction in histologically or radiologically measured liver steatosis grade (12 trials, N=765; SMD −1.5; 95% CI, −2.3 to −0.7).
- No significant association was noted between IWLI and histological scores for inflammation, intragastric ballooning, or fibrosis.
- Pharmacotherapy alone (orlistat, liraglutide, or sibutramine hydrochloride) did not improve steatosis, ALT, or AST.

LIMITATIONS:
- Included patients with type 2 diabetes that could confound the outcomes.
- Significant heterogeneity of BWLPs in type, duration, and format.
- Included one trial of sibutramine, which has been removed from the market.
- Evidence on bariatric surgery limited to only one trial. EBP

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Does continuous telemetry monitoring improve patient-centered outcomes in hospitalized general medical (noncardiac) patients?

CASE

A 67-year-old man is in the emergency department complaining of three days of cough with purulent sputum, shortness of breath, and chills and is found to have a three liter oxygen requirement. He has a medical history of coronary artery disease, type 2 diabetes mellitus, hypertension, and hyperlipidemia. His telemetry strip, troponin levels, and electrocardiogram performed in the emergency department are unremarkable. A chest X-ray confirms your suspicion of a community-acquired pneumonia. The decision is made to admit this patient to your service. As you submit your admit orders, do you place this patient on continuous cardiac telemetry monitoring?

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Bottom Line

Continuous cardiac telemetry monitoring of general medical (noncardiac) patients does not improve patient-centered outcomes such as readmission rates, incidence of in-hospital cardiac arrest, rapid response activations, or overall mortality. In fact, continuous cardiac telemetry without proper indication increases healthcare spending, may increase hospital length of stay, and can cause alarm fatigue, which may negatively affect patient care.

Review of Evidence

A 2017 multicenter retrospective cohort study analyzed outcomes with the use of telemetry monitoring in 765 adult patients hospitalized with respiratory infections who did not meet the 2004 American Heart Association (AHA) guidelines for telemetry, which generally restricts telemetry use to current or high-risk cardiac patients (defined as at risk for arrhythmia or ischemic events).[1] Patients who underwent telemetry monitoring (n=297) were compared with patients who received no monitoring (n=468). The median length of stay (LOS) was longer in patients who underwent telemetry (3 vs 2 days, $P<.0001$). No differences between cohorts were noted in 30-day readmission rates (0.6% vs 1.3%, $P=.32$), patient mortality while hospitalized (0.6% vs 1.3%, $P=.44$), mortality at 30 days (7.9% vs 7.7%, $P=.94$), or mortality at 90 days (14% vs 14%, $P=.99$). Further, there remained no significant difference after controlling for severity of illness. The authors concluded that patients hospitalized for respiratory infections who undergo telemetry without clear indications may face increased LOS without reducing their readmission risk or improving overall mortality.

A 2017 single-center, pre-post study evaluated outcomes after implementation of a new protocol for cardiac telemetry utilization on a progressive care unit (PCU) based on 2004 AHA guidelines.[2] At baseline, 77% of all admitted patients (total N not provided) were monitored with cardiac telemetry. Three months postintervention, data illustrated 67% cardiac telemetry assignment with a 10% reduction in telemetry usage ($P<.001$) with no associated increase in mortality rate ($P>.05$) compared with preintervention. A 42% cost reduction was achieved from downgrading patients' status from PCU to medical/surgical unit. Additionally, nurses reported 27% perceived reduction in alarm fatigue. The authors concluded that protocols to appropriately reduce cardiac telemetry use may reduce nurse alarm fatigue and cost per episode of care.

A 2019 single-center retrospective analysis assessed incidence of rapid response team (RRT) and code events in 210 hospitalized patients before, during, and after implementing an intervention to follow the 2004 AHA guideline, limiting telemetry to patients at risk of cardiac complications.[3] Outcomes were compared across a hospitalist group receiving the intervention and a nonhospitalist group that did not receive the intervention, both which are assigned patients at random. After adjusting for patient severity, RRT and code events were no different during the intervention to reduce telemetry use in the hospitalist group (incident rate ratio [IRR] 0.83; 95% CI, 0.54–1.3) or one year postintervention (IRR 1.1; 95% CI, 0.78–1.7). There was also no change in RRT and code events during the intervention for the nonhospitalist group (IRR 1.1, 95% CI, 0.56–2.2), although there was an increase in the postintervention period (IRR 1.8; 95% CI, 1.1–3.1). The authors concluded that there was not a significant change in RRT and code events after appropriate discontinuation of telemetry.

A 2014 single-center pre-post study assessed cost, RRT activations, code events, and deaths after an intervention to align telemetry ordering with 2004 AHA guidelines using order sets, which limited telemetry to patients at risk of cardiac complications.[4] Postimplementation, authors documented a reduction in the mean weekly number of telemetry orders from 1,032 to 593 ($P<.001$) and the mean duration of telemetry decreased from 58 to 31 hours ($P<.001$). The authors reported that hospital census, code blue, mortality, and rapid response team activation rates were stable throughout the observation period. The estimated total daily cost to deliver telemetry was $53.44 per telemetry patient; mean daily cost for non-intensive care unit cardiac telemetry decreased from $18,971 to $5,772 postintervention.

The AHA 2017 guidelines recommended against monitoring patients who are not at high risk for arrhythmia or cardiac ischemia (AHA Level of Evidence C—standard of care, consensus opinion of experts).[5]

CASE CONCLUSION

The patient was not placed on cardiac telemetry during the admission because he had no indication for monitoring according to the AHA guidelines. He had an uncomplicated hospital course and was discharged after three days. This avoided an unnecessary additional cost of $100 per day for telemetry monitoring. EBP

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CME

Does the risk of ACE-I–induced angioedema differ between Black and non-Black patients

EVIDENCE-BASED ANSWER

The incidence of ACE-I–induced angioedema is 3 to 5 times higher in Black than non-Black patients (SOR: **C**, 1 prospective and 1 retrospective cohort study). Among patients with heart failure, the incidence of ACE-I-induced angioedema is higher in blacks, athough the increased risk is not statistically significant (SOR: **C**, retrospective cohort study).

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A 2017 prospective cohort study (n=5,878,048) examined the incidence of angioedema among different ethnic groups prescribed an ACE-I, angiotensin receptor blocker (ARB), or beta-blocker.[1] Patients included Medicare beneficiaries, 65 years old and older, who filled a prescription for an ACE-I, ARB, or beta-blocker between March 2007 and March 2014. Patients were excluded if they had previously taken a study medication in the preceding 183 days, had a previous diagnosis of angioedema, or had filled a prescription for more than one study drug on the same day. Follow-up started the day after first prescription fill and continued for 365 days or until diagnosis of angioedema. The study stopped following participants if they had a 14-day or greater gap in prescription fill, addition of another study drug, disenrollment in Medicare, or death. The study outcome was diagnosis of angioedema (International Classification of Diseases, Ninth Edition [ICD-9] code 995.1), recorded at 1 to 30 days of treatment and 31 to 365 days of treatment, during an outpatient, inpatient, or emergency department visit. For new users of ACE-I (n=2,556,198), the crude angioedema rate per 1,000 person-years was 23.8 among Black patients (hazard ratio [HR] 5.72; 95% CI, 5.42–6.04), 4.03 among White patients (reference), 2.95 among Asian patients (HR 0.70; 95% CI, 0.55–0.90), 4.27 among Hispanic patients (HR 1.00; 95% CI, 0.84–1.19), and 3.65 for patients of all other ethnicities (HR 0.91; 95% CI, 0.73–1.12). Similar to all other groups, incidence of angioedema among Black patients was higher in the first 30 days (49.96, HR 20.22, $P<.001$) compared with days 31 to 365 (16.34, HR 10.12, $P<.001$). The study also noted an increased incidence of angioedema among Black patients taking a beta-blocker or ARB compared with other groups. Study limitations included limiting patients to those 65 years old and older and that compliance was measured in medication dispensing but not confirmed patient use. The authors made no attempt to provide a plausible mechanism for the association.

A 2018 retrospective cohort study (n=21,639) assessed the risk of angioedema among patients with heart failure started on an ACE-I.[2] Patient selection was based on ICD-9 code for heart failure, and patients were followed for a maximum of one year. The population was extracted from a commercial insurance health claims database, from January 2007 to March 2015, of which 11.5% of the patients were Black. The study group was predominately male (64.4%) and over age 65 years old (74.9%). Patients less than 18 years old, those with angioedema in the pre-index period, and those on an ACE-I or ARB in the previous 12 months were excluded. Angioedema was defined as ICD-9 code 995.1 in the medical record. In total, 40 patients had an angioedema event, including 32 non-Black and eight Black patients. The overall one-year incidence of angioedema per 1,000 patient-years was 3.3 (95% CI, 2.4–4.5). The incidence of angioedema in Black patients was 6.24 (95% CI, 3.12–12.5) versus 2.92 (95% CI, 2.06–4.13) among non-Black patients. Forty-three percent of angioedema events occurred in the first 30 days of ACE-I therapy. Although the incidence of angioedema was higher among Black patients, no statistically significant difference was noted in risk of angioedema between Black and non-Black patients (age-adjusted and sex-adjusted HR 1.94; 95% CI, 0.89–4.23). The study was limited, in that the population was all commercially insured and only captured those patients who had an ICD-9 billing code for angioedema. Additionally, an overall small number of Black patients enrolled in the study, and small overall number of angioedema events.

A 2008 retrospective cohort study (n=182) looked at patients evaluated by otolaryngology for angioedema at a tertiary care hospital between 1999 and 2004.[3] Patients included in the study had a clinical diagnosis of angioedema. Charts were reviewed for race, age, gender, and possible inciting agents, including medications, food allergies, and bee stings. Of the total study population, 72% of the patients with angioedema were Black, and 81% of the patients who had angioedema

attributable to ACE-I were Black. Black patients were three times more likely to develop ACE-I angioedema than all other patient groups (odds ratio [OR] 3.03; 95% CI, 1.54–5.94). Of all angioedema patients, 70% (95% CI, 62%–78%) of Black patients noted an ACE-I as the etiology compared with 44% (95% CI, 30%–59%) in the remainder of the study group. Limitations of this study included small size and that the link between angioedema and ACE-I was based on the patient's history and not an objective test. EBP

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Do community health worker interventions embedded in primary care improve chronic disease health outcomes in medically underserved patient populations?

EVIDENCE-BASED ANSWER

Maybe. Community health workers (CHWs) may improve adherence to follow-up visits and patient perceived control of their disease but do not consistently reduce emergency department visits in patients with chronic diseases (SOR: **C**, mixed evidence from 2 systematic reviews of various studies and single randomized controlled trial [RCT]). CHWs can increase screening for breast cancer up to 33% and help management of cardiovascular disease (SOR: **C**, qualitative evidence from a systematic review of RCTs, cohorts, and case-control studies).

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A 2016 systematic review of 34 studies (N=33,309) examined the role of Community health worker (CHW) interventions on various health care services.[1] A subanalysis evaluated five RCTs (N=1,496) that specifically examined CHWs use in caring for patients with at least one chronic disease. One RCT of 542 black Americans with type-2 diabetes received education and follow up care services with a nurse care manager (1 visit/year) and CHW (3 visits/year) over two years. After 24 months, no significant reduction was observed in emergency department visits compared with those not enrolled (risk ratio [RR], 0.77; 95% CI, 0.59–1.00). A second RCT enrolled 200 recently released prisoners with a chronic condition or older than 50 years. The CHW attended all parole meetings and offered a transitional visit within two weeks post release over 12 months. After 12 months, a significant reduction was observed in emergency department visits compared with those not enrolled (incidence rate ratio [IRR], 0.49; 95% CI, 0.34–0.70). A third RCT examined the completion of follow-up visits in patients with hypertension. Adult participants (n=421) with elevated blood pressure and income at 200% or less of the poverty level had CHWs set up, remind, and follow-up on patient clinical appoints and reduce barriers to transportation and childcare services. The intervention group's rate for completion of follow-up visits was significantly greater than the usual care group's rate (mean difference [MD], 39%; $P<.001$). The other two RCTs (N=333) measured outcomes for medication adherence but did not find significant changes after CHW intervention.

A 2018 multicenter, two-armed, single-blind RCT (n=592) examined the effectiveness of implementing a CHW for patients with two or more chronic illnesses.[2] Patients were recruited from three primary care facilities and included uninsured patients or those with public health insurance living in high-poverty areas. Patients were included if diagnosed with two or more of the following chronic diseases: hypertension, diabetes, obesity, and tobacco dependence. Patients were randomized to receive either tailored support from a CHW (n=304) or usual care (n=288). The primary outcome measured was self-reported physical health on the SF-12v2 Health Survey Physical Component Summary with higher scores indicating a better health status (score range 0–100), and secondary outcomes included chronic disease control and hospitalization rates. No significant change was observed in self-reported physical health between the CHW and the control groups at six months (MD, 0.6 vs 2.3; *P*=.06) and at nine months (1.8 vs 1.6; *P*=.89). However, patients receiving CHW support did report via a survey that general improvement was witnessed in their own management of their chronic diseases compared with the usual care group (odds ratio [OR], 1.8; 95% CI, 1.4–2.4). No significant difference was found in average length of stay for hospitalizations in the CHW group compared with the usual care group.

A 2016 systematic review of 61 studies (N=196,879) examined the evidence of CHW interventions within vulnerable populations for cost-effectiveness and patient outcomes stratified by chronic and nonchronic conditions.[3] The included studies were not described in detail but did include mainly RCTs and cohorts, with a few cross-sectional studies. Studies were included if CHWs served a primary role in the intervention of managing a chronic condition that is related to primary care. Thirty studies focused on cancer screening and 26 on cardiovascular disease prevention. The majority of interventions had only one CHW worker (82%), with 18% partnered with a primary care professional. The CHW functioned primarily as an educator in 79% of the studies, with 59% focused on counseling to address barriers and reinforce positive behaviors. Interventions included health coaching, health education, home visits, service linkages, and patient advocacy. Because of qualitative summaries and differences among scoring measures, no meta-analysis was conducted. Improvements in screening behaviors for patients with a CHW were seen in 70% of the studies focused on cancer, with increases in screenings observed between 6% and 33%. Sixteen studies (62%) found a positive change in cardiovascular risk reduction with CHW education directed toward elevated blood pressure or diabetic control. Only one study of the eight that measured cost-effectiveness found an overall cost reduction with implementing a CHW. EBP

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Among mothers working in the health care field, does a longer maternity leave decrease postpartum depression or burnout, compared to a shorter maternity leave?

EVIDENCE-BASED ANSWER

It is unclear. The duration of maternity leave does not seem to alter the risk of postpartum depression (SOR: **C**, 2 small cross-sectional surveys). However, in resident physicians, a longer maternity leave is associated with an overall, subjective improvement in well-being. (SOR: **C**, small cross-sectional survey). Those in procedural specialties are less likely to likely to report that consideration of maternity leave impacted their choice of specialty (SOR: **C**, cross-sectional survey).

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A 2019 anonymous cross-sectional survey (N=204) completed by practicing female OB-GYNs compared postpartum experiences between resident OB-GYNs versus nonresident OB-GYNs.[1] Both nonresident OB-GYNs (n=155) and resident OB-GYNs (n=49) responded on their feelings of depression. The responses were then compared with whether or not OB-GYNs received at least six weeks of maternity leave. Responses were self-reported and not based on a clinical diagnosis. A larger proportion of resident mothers (26%) reported feelings consistent with postpartum depression compared with nonresident mothers (16%). Resident mothers were also significantly more likely to receive less than six weeks of maternity compared with nonresident mothers (odds ratio [OR], 2.8; 95% CI, 1.6–5.0). However, overall, no significant difference was found in self-reported feelings of postpartum depression between resident and nonresident mothers (OR, 1.8; 95% CI, 0.93–3.6). Limitations included lack of representative subjects of all physician mothers and self-reporting bias.

A 2018 survey-based cross-sectional study (n=214) analyzed the length of maternity leave effect on maternal and infant well-being at a single academic hospital.[2] The surveys were sent to all female residents at the academic center regardless of residency type and child-bearing status. In total, 36% of residents took 4–8 weeks of maternity leave during training and 30% took less than four weeks. Outcomes were measured based on Edinburgh postpartum depression screening, Likert satisfaction scales, and qualitatively by free text responses. No significant difference was found between residents who took a maternity leave of eight weeks or greater compared with those less than eight weeks for postpartum depression (n=13, 70% vs 33%; *P*=.51), positive colleague support (n=25, 88% vs 78%; *P*=.60), program director support (n=25, 88% vs 67%; *P*=.31), or satisfaction with their decision to have a child during training (n=25, 75% vs 56%; *P*=.39). However, there was a subjective improvement in overall well-being associated with those who took a longer maternity leave based on the free-text response section.

A 2014 cross-sectional survey (N=1,541) analyzed data from a large-scale national survey among physician mothers to define the personal, professional, and financial impact of maternity leave.[3] The survey was made available to members of the Facebook Physician Mom Group, a group exclusive to female physicians with children. Of this group, 393 physicians (26%) identified in procedural fields, including OB-GYN, surgery and surgery subspecialties, and anesthesiology and 1,148 (74%) physicians identified as nonprocedural specialties. Female physicians working in procedural fields were significantly more likely to report a maternity leave of less than eight weeks compared with those in nonprocedural fields (OR, 1.7; 95% CI, 1.1–2.5). Proceduralists were significantly less likely to report that pregnancy or child-rearing impacted their choice of specialty (OR, 0.2; 95% CI, 0.2–0.3) and were more likely to agree with the statement that they wished they had chosen a less demanding specialty or job (OR, 2.3, 95% CI, 1.8–3.0) compared with nonprocedural physician mothers. EBP

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Is increased social media use associated with depression in teenagers?

EVIDENCE-BASED ANSWER

Perhaps. Increased social media use has been associated with depression in teenagers and adolescents (SOR: **C**, conflicting evidence from a cohort and 2 case-control studies). Any association does not prove a causal link.

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A 2018 UK prospective cohort study of 19,244 children investigated the association between social media use and mental health.[1] Children were all 14 years old and completed the Mood and Feelings Questionnaire, which comprised 13 items including depressive symptoms, social media use, online harassment, sleep duration, sleep latency, sleep disruption, self-esteem, happiness with appearance, and body weight satisfaction. Overall, girls reported more social media use than boys, 43% versus 22% of greater than three hours daily. Increased social media use was associated with experiences of online harassment, short sleep hours, longer sleep latency, sleep disruption, being unhappy with the appearance, and body weight dissatisfaction. Teens who reported more than five hours of social media use per day were significantly more likely to have a high depression scores compared with those using less than five hours (50% vs 35%; $P<.001$).

A 2016 case-control study (N=467) examined the effect of social media use on poor sleep quality, anxiety, depression, and low self-esteem in adolescents.[2] Participants 11 to 17 years old were recruited from a single Scottish secondary school. Adolescents were administered numerous validated questionnaires evaluating sleep quality, anxiety/depression, and self esteem. Emotional investment in social media was evaluated using a 5-point Likert scale, from "strongly disagree" to "strongly agree", with higher scores indicating a greater level of emotional investment. Responses were collected over a rolling period of the school year in both online and pencil-and-paper format. Resulting scores of these surveys were used to compare social media use to aspects of mental health with larger r scores indicating stronger correlation. Increased levels of social media use were significantly associated with poorer sleep quality (r=0.24; $P<.001$), higher anxiety levels (r=0.21; $P<.001$), and higher depression levels (r=0.11; $P<.01$).

A 2017 three-phased case-control study (N=151) tracked the daily experiences, behaviors, and emotions of young adolescents regarding social media use and mental health.[3] Participants had a mean age of 13 years and were considered to be high risk for mental health problems. High-risk behavior included inattention or hyperactivity issues, substance abuse or exposure to, and general behavioral issues. Adolescents were surveyed at baseline, at around 30 days, and at 18-month follow-up. Adolescents reported an average of 2.3 hours of social media use and 41 text messages daily. After a total of 4,300 study days, respondents reported at least one anxiety symptom on 32% of days and at least one depression symptom on 27% of days. However, the final multivariate Poisson model revealed no significant correlation between social media time usage and symptoms of anxiety ($\beta=-0.05$; 95% CI, –0.11 to 0.01) or depression ($\beta=-0.05$; 95% CI, –0.11 to 0.01). EBP

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Is exercise in pregnancy associated with negative neonatal outcomes?

EVIDENCE-BASED ANSWER

Probably not. Combination exercise, including aerobics, strength training, and stretching does not result in increased likelihood of macrosomia (SOR: **A**, consistent randomized controlled trials [RCTs]) or preterm birth and preeclampsia (SOR: **B**, single RCT). Additionally, exercise may reduce the incidence of hypertension and excessive weight gain for mothers during pregnancy (SOR: **B**, single RCT).

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A 2016 randomized controlled trial (RCT; n=765) examined the relationship of supervised exercise on pregnancy-induced hypertension and negative neonatal outcomes.[1] Women were Spanish speaking, white, and 27 to 36 years old with uncomplicated singleton pregnancies. Patients with type 1 or type 2 diabetes, poorly controlled gestational diabetes, or who had a history of preterm deliveries were excluded. Women were randomized to either a combination of aerobic exercise, dance, and muscular strength training for three days a week at about 50 minutes per session (n=382) or a control group receiving only advice on the benefits of physical activity (n=383). Those in the exercise group began sessions between nine and 11 weeks of gestation and continued till the end of the third trimester. Hypertension was defined as systolic blood pressure (BP) of greater than 140 mmHg and/or diastolic BP greater than 90 mmHg on two separate occasions. Results were controlled and adjusted for by differences in age, smoking status, occupation, body mass index (BMI), and activity levels pre pregnancy. After adjustment, the control group was significantly more likely than the exercise group to develop hypertension (adjusted odds ratio [aOR], 2.9; 95% CI, 1.3 to 6.8), to gain excessive weight (aOR, 1.5; 95% CI, 1.1 to 2.0), and to give birth to an infant with macrosomia (aOR, 2.5; 95% CI, 1.03–6.20).

A 2015 RCT (n=639) evaluated the efficacy of implementing supervised exercise to prevent negative maternal and newborn health outcomes.[2] Pregnant women were 18 years or older recruited from local clinics in a city in Brazil. Patients were normotensive with prepregnancy BMI between 21 and 35 kg/m^2 and had singleton pregnancies. Exclusion criteria included preexisting hypertension, cardiovascular disease, diabetes, and history of preterm birth or miscarriage. Randomization was conducted in a 2:1 control-to-treatment ratio to increase power and precision of outcomes. The treatment group (n=213) exercised three times per week for at least 16 weeks between 13 and 36 weeks of gestation. The workout sessions were structured, individually supervised, with moderate intensity exercise for one hour, three days per week. Each session included aerobic, strength, and stretching exercises. Participants in the intervention group received a mean of 48 training sessions. Adherence was determined by at least 70% attendance to the sessions. Both intervention and control groups received standard antenatal care. The control group (n=426) was encouraged to continue normal daily activities. Of the initial 639 women, only 594 (198 intervention, 396 control) were included in the statistical analysis due to dropout. Of those who were included in the intervention analysis, only 40% had at least 70% adherence to the exercise sessions. Compared with the control group, the exercise group had no significant increase in preterm birth of 37 weeks or less (OR, 1.1; 95% CI, 0.7–1.8), preeclampsia (OR, 1.0; 95% CI, 0.6–1.9), gestational weight gain (mean difference [MD], 0.4 kg; 95% CI, –0.6 to 0.8 kg), or birth weight (MD, 20 g; 95% CI, –62 to 100 g). EBP

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Is the risk of cesarean delivery higher with term elective induction using oxytocin or misoprostol?

EVIDENCE-BASED ANSWER

There is no difference in cesarean delivery rates when using oxytocin or misoprostol in term elective induction. (SOR: A, consistent, randomized controlled trials).

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A 2008 randomized controlled trial (RCT) of women (n=327) with cephalic presentation, singleton pregnancies being induced with an unfavorable cervix (Bishop score <5) evaluated vaginal misoprostol versus continuous oxytocin IV infusion for rates of vaginal delivery.[1] Patients were on average 27 years old with a mean gestational age of 40 weeks and mean Bishop score of two. Of the women, 42% were nulliparous and 88% to 92% were Hispanic. Patients in the oxytocin group (N=163) began oxytocin infusion, with parity determining dosing: 4 mU/min for nulliparous and 2 mU/min multiparous. Each group could be increased every 15 minutes to a maximum rate of 40 mU/min. Patients in the misoprostol group received 25 μg intravaginally every four hours, with a maximum of three doses until Bishop score was at least seven or reaching active labor. Additionally, 88% of patients in the misoprostol group were given oxytocin following cervical ripening. No difference was observed in the anesthesia type used or time before epidural placement. Indications for C-section included nonreassuring fetal heart tones, labor dystocia, malpresentation, and placental abruption. The cesarean delivery rate did not differ significantly between groups (oxytocin 13% vs misoprostol 19%; $P=.17$). Maternal complications included tachysystole, intraamniotic infection, postpartum hemorrhage, blood transfusion, endometritis, and uterine rupture. None of these outcomes showed statistical association with the method of induction. This study did not, in the end, recruit the sample size predetermined to yield significant power.

A 2004 RCT of 70 women with cephalic presentation singleton term pregnancies (Bishop score ≤6) evaluated the efficacy of oral misoprostol (n=36) versus continuous IV oxytocin (n=34) for labor induction.[2] Exclusion criteria included cervix favorable for amniotomy (Bishop score ≥6), nonvertex presentation, intrauterine demise, previous uterine scar, oligohydramnios, intrauterine growth retardation, multifetal pregnancy, clinical evidence of cardiopulmonary, hepatic, renal disease, electrolyte abnormalities, preeclampsia, and eclampsia. Patients were 25 years old on average with a mean gestational age of 40 and 39 weeks (37–42 weeks). Patients received 50 μg of oral misoprostol every four hours for maximum of five doses until amniotomy, active labor, or spontaneous membrane rupture. Patients in this group were allowed to receive oxytocin if contractions were inadequate; however, only one patient required oxytocin. The other patients received oxytocin 2 mU/min and increased 2 mU/min every 15 minutes until "optimal response," then continued until delivery. Inability to deliver vaginally at 24 hours was defined as "failure." Mean Bishop score of patients before induction was 3.5, which did not differ significantly between the groups. No difference was found in cesarean section rates between misoprostol and oxytocin groups (8.3% and 5.9%; $P=.69$). No differences was observed in neonatal or maternal outcomes or complications. A limitation of this study was small sample size. EBP

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Does supplementation with myo-inositol reduce the risk of developing GDM?

EVIDENCE-BASED ANSWER

Maybe. Overall, supplementation with myo-inositol does not appear to lower rates of gestational diabetes (GDM); however, 2 g myo-inositol twice daily during pregnancy is associated with a 66% lower rate of GDM (SOR: **B**, limited-quality meta-analysis of randomized controlled trials [RCTs]). In women at high risk for GDM, prenatal supplementation with myo-inositol twice daily compared with control is associated with a 29% lower risk of abnormal two-hour glucose tolerance test at 24 to 28 weeks (SOR: **B**, RCT).

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A 2019 meta-analysis of five randomized controlled trials (RCTs; N=965) evaluated the effects of inositol supplementation during pregnancy.[1] Four of the five studies included only women with singleton pregnancies and two of the studies included only women with first-degree relatives who had type II diabetes. Four of the five studies specified body mass index (BMI) as an inclusion criterion with BMI <30 kg/m^2, BMI 25 to 30 kg/m^2, BMI ≥30 kg/m^2, and BMI >25 kg/m^2, and the last study did not have a BMI requirement, but their study population had a mean BMI of 26 kg/m^2. Three of the studies compared 2 g myo-inositol twice daily plus 200 mcg folic acid versus 200 mcg folic acid twice daily. Another study compared 1.1 g myo-inositol plus 27.6 mg D-chiro inositol versus 400 mcg folic acid daily, whereas another study compared 2 g myo-inositol plus 400 mg D-chiro inositol plus 400 mcg folic acid plus 10 mg manganese daily versus an unspecified control group. Inositol supplementation began at 10 to 24 weeks' gestational age. The primary outcome was the rate of gestational diabetes (GDM), diagnosed by the International Association of Diabetes and Pregnancy Study Groups Consensus Panel 2010 criteria. No difference was noted in rates of GDM among those who took inositol supplementation compared with control (126 of 1,000 vs 227 of 1,000; 4 trials, N=848; odds ratio [OR] 0.49; 95% CI, 0.24–1.03; I^2=73%). Secondary outcomes showed decreased rates of preterm deliveries for inositol (4 trials, N=829; OR 0.35; 95% CI, 0.17–0.74; I^2=0%). However, in subgroup analysis, the GDM rate was lower in the myo-inositol group receiving 4 g total per day versus placebo (3 trials, N=608; OR 0.34; 95% CI, 0.21–0.53; I^2=17%). No difference was observed in GDM rates for the group receiving 1.1 g myo-inositol plus 27.6 g D-chiro inositol per day versus control (1 trial, n=240; OR 1.34; 95% CI, 0.68–2.64). No adverse effects of inositol supplementation, industry funding, or conflict of interest were reported. The authors note that the overall quality of evidence was very low because of high risk of bias.

A 2018 RCT (n=157) at a single center in Italy was performed among pregnant women at high risk for GDM to test whether various inositol supplements reduces the risk of developing GDM.[2] Women with singleton pregnancies and elevated first-trimester blood glucose levels (92–125 mg/dL) were included. Women with a BMI >35 kg/m^2, multiple gestations, pregestational diabetes, or less than 18 years old were excluded. The range of ages of the patients in the study was 28 to 39 years old. All the patients were given nutrition and exercise counseling and given pills to take daily for the duration of their pregnancy. The control group received 400 mcg folic acid daily. One group received 4 g myo-inositol and 400 mcg folic acid daily in separate pills to be taken within six hours of each other. Another group received 500 mg D-chiro inositol and 400 mcg folic acid in one capsule daily. A third group received 1.1 g myo-inositol and 27.6 mg D-chiro inositol daily in separate pills to be taken within six hours of each other. The primary outcome was an abnormal maternal two-hour oral glucose tolerance test (OGTT) at 24 to 28 weeks of gestational age, defined as one or more blood glucose levels greater than 92 mg/dL fasting, 180 mg/dL at one hour, and 153 mg/dL at two hours. A significantly lower incidence of abnormal OGTT resulted for the myo-inositol group in comparison with all the other groups: 5.1% (2 of 39) in the myo-inositol group, 62% (32 of 52) in the control group, 34% (11 of 32) in the D-chiro inositol group, and 38% (13 of 34) in the mixed inositol group (P<.001 for myo-inositol compared with each group). In addition, neonates born to mothers in the myo-inositol group had significantly lower rates of hypoglycemia: zero in the myo-inositol group, 11 in the control group, five in the D-chiro inositol group, and three in the mixed inositol

group (P=.023 for myo-inositol compared to each group). No adverse side effects due to therapy were reported. No blinding was described in the study; therefore, the results are of limited quality. EBP

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Do financial incentives increase smoking cessation rates among pregnant women?

EVIDENCE-BASED ANSWER

Yes. Financial incentives increase smoking cessation rates among pregnant women compared with those not incentivized (SOR: **A**, meta-analysis of randomized controlled trials). Clinicians should provide behavioral interventions, which can include financial incentive programs, to pregnant women to assist with smoking cessation (SOR: **C**, expert consensus).

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A 2019 systematic review and meta-analysis of 10 randomized controlled trials (RCTs; n=2,571) examined the use of financial incentives to promote smoking cessation in pregnant women.[1] Only nine RCTs had usable data (N=2,273), with eight of these studies performed in the United States and one in the United Kingdom. Participants were adult pregnant smokers in public and private antenatal clinics, obstetric offices, and community antenatal programs. The intervention groups received cash payments or vouchers for goods or services as the incentive, which, in four studies (N=331), increased in value for longer periods of abstinence from smoking. Both the intervention and the control groups received practical cessation support, which varied between studies, but could include self-help materials, a brief motivational interviewing session, web-based cessation programs, or telephone support. In six studies (N=2,160), control groups also received fixed financial incentives for participation alone (not contingent on cessation or abstinence). Half of these studies reported noncontingent incentives that were relatively equivalent to that received in their intervention groups, whereas in the other studies, the fixed incentives were significantly less than in their intervention groups. Participants only received the incentives with a biochemically verified abstinence test. Abstinence was measured at the closest visit to birth, with some studies tracking into 10 to 24 weeks postpartum. Incentives were significantly more likely to improve smoking cessation rates among pregnant smokers at their longest follow-up with a number needed to treat of 10 (9 studies, N=2,273; risk ratio [RR] 2.4; 95% CI, 1.5–3.7) compared with those who were not incentivized. No significant difference was noted between contingent incentives and fixed incentives for abstinence rates (3 trials, N=225; RR 3.3; 95% CI, 0.97–11). Limitations included the inability to determine effect between high- or low-value incentives, and lack of adequate randomization of groups in some studies.

A 2015 evidence-based guideline from the United States Preventative Services Task Force recommended all clinicians ask pregnant women about tobacco use, instruct them to quit smoking, and provide behavioral interventions to assist with quitting (grade A, substantial high certainty evidence).[2] Behavioral interventions recommended by the task force included behavioral health counseling, feedback, health education, social support, and financial incentives. EBP

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Does the addition of OMT in the antepartum or intrapartum period decrease the duration of labor compared with standard obstetrical management alone?

EVIDENCE-BASED ANSWER

It may depend on the period of labor. The addition of osteopathic manipulative treatment (OMT) to usual obstetric care beginning at 30 weeks' gestation can result in an increased incidence of labor lasting 20 hours or longer (SOR: **B**, single randomized controlled trial). However, daily OMT during intrapartum management may decrease overall labor duration in both primiparous and multiparous women (SOR: **C**, prospective observational study).

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A 2016 randomized controlled trial (n=380) evaluated the role of osteopathic manipulative treatment (OMT) on the incidence of prolonged labor (>20 hours) in healthy women 18 to 35 years old.[1] Women had a mean age of 24 years old and were at 30 weeks' gestation upon enrollment. Women deemed to be at high risk for abruptio placenta, placenta previa, severe preeclampsia, vaginal bleeding, etc, were excluded. Patients were randomized to either antepartum OMT with usual care (n=136), placebo ultrasound plus usual care (n=131), or usual care only (n=133). Participants in each group were scheduled for seven visits over nine weeks starting at 30 weeks of gestation that lasted for 20 minutes. Patients in the OMT group were treated with techniques including myofascial release, articulatory treatment, muscle energy treatment, balanced ligamentous tension, and soft tissue treatment. All treatments were provided by physicians board-certified by the American Osteopathic Board of Neuromusculoskeletal Medicine. Those in the ultrasound group had an ultrasound probe applied in the same regions as the OMT treatments. High-velocity, low-amplitude treatments were excluded. Patients in the OMT group were significantly more likely to have prolonged labor compared with patients receiving usual obstetrical care only (odds ratio [OR] 2.3; 95% CI, 1.1–9.8) and patients in the ultrasound group (OR 4.0; 95% CI, 1.7–9.8).

A 2017 prospective observational study investigated whether intrapartum OMT affected duration of labor compared with obstetrical management alone in women who were expected to deliver vaginally.[2] A total of 100 women were enrolled in the study from a single institution and were divided into two patient groups: standard obstetrical management alone (n=50) and standard obstetrical management during labor with adjunctive OMT (n=50). The women in the adjunctive OMT group received a once-daily, 20-minute intrapartum OMT session that was performed by the same provider. Obstetrical management decisions were made by the same osteopathic attending. The median age for patients in both groups was 28 years old, and all women received epidural anesthesia and intravenous oxytocin at some point during their labor. The OMT techniques used included suboccipital decompression, thoracic inlet release, rib raising, paraspinal inhibition, and sacral inhibition. Primiparous and multiparous women who received intrapartum OMT had significantly shorter durations of labor compared with women who received standard obstetrical management alone (11 vs 17 hours, $P=.03$). EBP

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What are the risks and benefits of discontinuing oxytocin after reaching the active phase of labor in patients undergoing labor induction or augmentation?

EVIDENCE-BASED ANSWER

Discontinuing oxytocin after the active phase of labor is established and provides moderately decreased risk of uterine tachysystole with abnormal fetal heart rate and abnormal intrapartum cardiotocography (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). However, it does not significantly reduce the risk of cesarean delivery and has no effect on risk of chorioamnionitis, labor pain, APGAR scores, or cord gases (SOR: **A**, meta-analysis of RCTs). Elective oxytocin discontinuation should be considered to reduce fetal heart rate abnormalities and uterine tachysystole (SOR: **C**, expert consensus).

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A 2018 systematic review and meta-analysis (N=1,888) of 10 randomized controlled trials examined birth outcomes in patients undergoing labor induction where intravenous (IV) oxytocin was discontinued once the active phase of labor was established.[1] Women included had a singleton pregnancy who underwent induction of labor with oxytocin during the latent phase of labor. Women were 22 to 31 years old, with 45% to 65% being nulliparous, and a prepregnancy body mass index of between 22 and 32 kg/m^2. Patients were randomized to receive continuous oxytocin during the active phase of labor (n=896) or oxytocin was discontinued during the active labor phase (n=888). The active labor was defined as well established contractions and cervix dilatation of at least 5 cm. Outcomes measured can be seen in **Table**. Compared with women given continuous oxytocin, women who had oxytocin discontinued had a significantly reduced risk of uterine tachysystole with abnormal fetal heart rate, decreased uterine tachysystole independent of fetal heart rate, and reduced suspicious or pathological intrapartum cardiotocography (see **Table**). Measured outcomes without significant difference included cesarean section rate during active phase of labor, chorioamnionitis, use of analgesia and epidural during labor, APGAR scores of less than seven at five minutes, and acidotic cord gases at birth with arterial umbilical pH less than 7.1.

TABLE Summary of outcomes comparing discontinuation of IV oxytocin augmentation versus continuation of IV oxytocin in the active phase of labor[1]

Outcome	No. of RCTs	No. of Participants	Risk ratio (95% CI)
Uterine tachysystole with abnormal FHR	3	486	0.15 (0.05–0.46)
Uterine tachysystole	4	728	0.45 (0.30–0.68)
Cardiotocography abnormalities	7	1,390	0.65 (0.51–0.83)
Cesarean delivery	4	787	0.92 (0.65–1.3)
Chorioamnionitis	1	252	2.3 (0.99–5.5)
Use of analgesia and epidural during labor	3	556	1.0 (0.95–1.1)
"APGAR" <7 at 5 min	4	993	0.78 (0.27–2.2)
Acidotic cord gas	4	873	1.0 (0.50–2.1)

APGAR = appearance, pulse, grimace, activity, and respiration; FHR = fetal heart rate; RCTs = randomized controlled trials.

A 2017 evidence-based guideline from the Queensland Statewide Maternity and Neonatal Clinical Network recommended the elective discontinuation of oxytocin infusion after active labor is established, defined as contractions being well established and cervix dilated to (no strength of recommendation given).[2] Discontinuation was recommended to reduce the incidence of fetal heart rate abnormalities and uterine tachysystole. EBP

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Does breastfeeding for at least three months decrease the risk of childhood asthma?

EVIDENCE-BASED ANSWER

Probably. Any breastfeeding for at least three months is associated with a reduced risk of asthma in children less than seven years old but not in children seven years old or older (SOR: **B**, meta-analysis of cohorts, cross-sectionals, and case-control studies). Children at risk for type 1 diabetes have a lower risk of asthma at age five if breastfed more than 9.5 months compared with less than five months (SOR: **B**, single cohort study). Exclusive breastfeeding up to six months decreases the risk of asthma at age 3 to 5 years old (SOR: **C**, single cross-sectional study).

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A 2014 systematic review and meta-analysis (N=823,013) of 57 cohort, 47 cross-sectional, and 13 case-control studies evaluated the association between breastfeeding and the risk of asthma or wheezing in children.[1] Children in these studies ranged from newborns to school aged at the time of enrollment. Breastfeeding duration for infants ranged from never to greater than six months. Any children with family history of asthma or studies of those already displaying wheezing signs were excluded. Duration of follow-up was variable due to the variety of study types and was not specifically reported. Researchers performed a sub-analysis of five studies specifically examining inclusive breastfeeding for at least three months. In this sub-analysis, breastfeeding for at least three months significantly decreased the rate of asthma ever compared with less or no breastfeeding in those 0 to 2 years old (odds ratio [OR] 0.59; 95% CI, 0.5–0.7) and in those three to six years old (OR 0.84; 95% CI, 0.76–0.92) but not for older children aged greater than seven years old (OR 0.86; 95% CI, 0.73–1.0).

A 2012 prospective cohort study (n=3,142) investigated the relationship between breastfeeding duration and maternal diet on the later development of asthma in children at risk for type 1 diabetes.[2] Participants were infants born with human leukocyte antigen-conferred susceptibility to type 1 diabetes at three university hospitals in Finland. Breastfeeding (median duration: 7 months) was assessed as part of standard dietary questionnaires at three, six, and 12 months of age. Breastfeeding cutoffs for comparison were determined after statistical analysis rather than being predefined. Asthma diagnosis was physician-confirmed with wheezing or the use of asthma medications in a 12-month period and collected via a questionnaire at five years of age. All children in the study with relevant endpoint data were included (83% of the total). Children breastfeeding for less than five months had an increased rate of asthma versus children breastfeeding for 10 months or more (adjusted hazard ratio 1.9; 95% CI, 1.2–3.0). However, no increased risk was noted for children with exclusive breastfeeding of less than three months compared with those breastfed more than three months. Based on these results, the authors concluded that "total breast-feeding, rather than its exclusivity, might be a more important determinant of asthma in childhood."

A 2019 cross-sectional study (n=15,642) examined the relationship of breastfeeding on asthma in children 3 to 5 years old while controlling for adverse childhood experiences.[3] Participants were recruited from the 2011 to 2012 United States National Survey of Children's Health. Children who were never breastfed (n=3,832) were compared with children who were exclusively breastfed up to six months of

age, breastfed with supplementation up to six months of age, breastfed with supplementation for greater than six months to less than 12 months, and breastfed with supplementation for 12 months or longer (n=11,810). The primary outcome was physician-diagnosed asthma at the time of the survey. Results were controlled and adjusted for potential confounding variables such as sex, birth weight, race, maternal education, household income, and adverse childhood events and then reported as adjusted-incidence risk ratios (aIRR). Exclusive breastfeeding for 1 to 6 months was associated with a reduced risk of asthma (aIRR 0.64; 95% CI, 0.46–0.88), whereas breastfeeding for 1 to 6 months with supplementation was not (aIRR 1.1; 95% CI, 0.91–1.4) compared with those never breastfed. Breastfeeding for 6 to 12 months with supplementation was more strongly associated with decreased risk of asthma (aIRR 0.5; 95% CI, 0.35–0.7), whereas breastfeeding for longer than 12 months was about the same compared with children never breastfed. EBP

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Are probiotics as effective as metronidazole for the treatment of symptomatic bacterial vaginosis?

EVIDENCE-BASED ANSWER

Probably. Certain strains of probiotics perform as well as metronidazole for treatment of bacterial vaginosis (SOR: **B**, systematic review of randomized controlled trials [RCTs] and single RCT). There may be benefit to adding probiotics containing lactobacillus species with metronidazole for the treatment of bacterial vaginosis (SOR: **B**, systematic review of RCTs). Intermittent use of lactobacilli-containing vaginal probiotics may also reduce bacterial vaginitis recurrence (SOR: **C**, small RCT).

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A 2013 systematic review (N=1,033) of eight randomized controlled trials (RCTs) evaluated probiotics alone or in conjunction with standard antibiotics for the treatment of symptomatic bacterial vaginosis.[1] Participants were fertile, pregnant or nonpregnant female patients from Nigeria and other nonspecified countries worldwide with at least two of Amsel criteria for the diagnosis of bacterial vaginosis. Amsel criteria includes thin homogenous vaginal discharge, vaginal pH higher than 4.5, "fishy" odor of vaginal fluid after addition of 10% KOH (whiff test) and presence of clue cells on microscopic evaluation of saline wet preparations. Three trials were identified that specifically evaluated the use of oral metronidazole and probiotics. The first trial of 40 women examined the efficacy of daily vaginal probiotic capsules compared with 0.75% metronidazole gel applied twice daily over five days. After 30 days, the probiotic group did not have a significantly higher cure rate for vaginosis compared with the metronidazole group (65% vs 33%, $P=.06$). The second trial included 125 women who were given oral metronidazole 500 mg twice daily for seven days in conjunction with oral capsules of probiotics or placebo twice daily for 30 days starting on day 1 of metronidazole treatment. Patients treated with combination metronidazole and probiotics achieved a cure rate significantly higher than the metronidazole-only group (88% vs 40%, $P<.01$). The last trial included 268 women who were given oral metronidazole 400 mg twice daily for seven days followed by vaginal pessary containing probiotic and estriol for 12 days or placebo. No significant difference was observed between patients in the combination metronidazole and

probiotic group compared with those in the placebo group (72% vs 73%, $P>.05$).

A 2020 RCT (n=68) from Rwanda examined the intermittent use of two vaginal probiotics in comparison with oral metronidazole to prevent the recurrence of microbiological bacterial vaginosis after metronidazole treatment.[2] Cure of bacterial vaginosis was measured by Nugent score or modified Amsel criteria. Participants were women 18 to 45 years old who were at high urogenital infection risk (defined as having had more than 1 sexual partner, having been treated for a sexually transmitted infection, or having been treated for bacterial vaginitis in the last 12 months), confirmed HIV-negative status, and not pregnant. Women were excluded if the clinician observed genital ulcers, condylomata, or other genital abnormalities, or if they had a history of undiagnosed vaginal bleeding. Women were randomized to one of four groups containing 17 patients in each: behavioral counseling only, counseling plus 500 mg oral metronidazole twice weekly, counseling plus Ecologic Femi + vaginal capsule (1.5×10^9 colony-forming unit [CFU] of multiple lyophilized bacteria) once per day for the first five days followed by three times weekly, and counseling plus GynLP (1.6 × 109 CFU of Lcr35, a culture of *Lactobacillus rhamnosus*) once every four days. Participants applied the first dose of their intervention under direct observation at the enrollment visit, continued treatments for two months, and returned to the clinic after seven days, one month, two months, and six months for vaginal microbiota assessments. Assessments included gram stain Nugent scoring and 16S rRNA gene qPCR and HiSeq sequencing. After six months, compared with the control group, the incidence of bacterial vaginitis was significantly lower in the metronidazole group (10.2 vs 1.4 person-years, $P<.01$) and in the Ecologic Femi+ group (10.2 vs 3.5 person-years, $P=.04$). No difference was noted between the control group and those in the GynLP group. EBP

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Do probiotics reduce the frequency of urinary tract infections in women?

EVIDENCE-BASED ANSWER

Yes. In female patients, *Lactobacillus* supplementation reduces the recurrence of urinary tract infections (UTIs) compared with placebo (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). In postmenopausal women with a history of UTI, *Lactobacillus* supplementation is about as effective as trimethoprim-sulfamethoxazole prophylaxis and does not result in the development of antibiotic-resistant organisms (SOR: **B**, single RCT).

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A 2018 meta-analysis of nine clinical trials (N=726) examined the efficacy of *Lactobacillus* to prevent urinary tract infections (UTIs) in women.[1] A subanalysis of six randomized controlled trials (N=620) that specifically examined *Lactobacillus* versus a placebo were identified. Trial patients varied greatly in age, ranging from 18 to 80 years, with five trials including premenopausal and one trial including postmenopausal women. Patients experienced at least 1 to 4 UTIs in the preceding 12 months. Formulation of the different lactobacilli strains included oral or vaginal suppository with dosing ranging from 10^8 to 10^9 colony forming units (CFU) of *Lactobacillus* spp. Frequency of probiotic dosing ranged from twice daily to twice weekly and treatment duration ranged from four weeks to 12 months with a follow-up from 6 to 12 months. After pooling of all six trials (N=620), women treated with *Lactobacillus* supplementation had a significantly decreased risk for recurrent UTIs compared with the placebo group (risk ratio, 0.68; 95% CI, 0.44–0.93).

A 2012 randomized, double-blind, noninferiority trial (n=252) included in the 2018 meta-analysis above investigated the clinical recurrence of UTI and antibiotic resistance in postmenopausal women treated with 12 months of trimethoprim-sulfamethoxazole (TMP-SMX) compared with *Lactobacillus* spp.[2] This trial was specifically summarized because of inclusion of an active control. Patients were postmenopausal women with history of at least three symptomatic UTIs in the preceding year. Women who were premenopausal and with asymptomatic UTIs were excluded. The first group received 480 mg of TMP-SMX every night (n=115), whereas the comparison group received twice daily 10^9 CFU of *Lactobacillus* for 12 months (n=123). After 12 months of prophylactic treatment, the *Lactobacillus* prophylaxis group did not significantly differ from the TMP-SMX group in recurrence of UTIs (clinical recurrence 2.9 vs 3.3; $P>.05$). However, prophylaxis with TMP-SMX led to an increase in antibiotic resistance to TMP-SMX, trimethoprim, and amoxicillin to 80% in 95% of women, compared with no increase in antibiotic resistance with *Lactobacillus* prophylaxis. EBP

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What is the best primary care screening method for fall risk in the elderly population?

EVIDENCE-BASED ANSWER

It is unclear. Although many screening tools exist to evaluate fall risk in the elderly, no one tool has good diagnostic accuracy. (SOR: **B**, multiple systematic reviews of small cohort studies). Screening tests may be more useful when examining patients with cognitive impairment or a history of falls in the past (SOR: **B**, systematic review of cohorts and expert consensus). Collecting a history of falls within the past year in patients aged 65 years and older is recommended to determine those at high risk of falls (SOR: **C**, expert consensus).

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A 2018 systematic review and meta-analysis of 23 prospective cohorts (N=5,312) explored the frequency, diagnostic accuracy, and validity of several, different, fall risk assessment tools.[1] Almost all studies enrolled seniors aged 60 years or older independently living in the community. The Berg balance scale (BBS) and Timed Up and Go Test (TUG) were the most studied assessment tools used for community-dwelling elderly. Many other tools were analyzed but in low numbers of patients or studied only in hospitalized patients. The BBS tests 14 balance-related tasks, scoring each from 0 to 4 points for a maximum total of 56. Scores less than 20 would represent wheelchair bound, scores of 20 to 40 indicate walking with assistance, and scores more than 40 represent independent walking. The TUG was designed as a functional mobility test and requires rising from a chair, walking 3 m, turning, returning to the chair, and sitting down. Although commonly used as a physical test to screen for risk of falling, it has not been validated and has no defined normal or abnormal completion time. After pooling of five studies (N=570), the BBS had moderate diagnostic accuracy for ruling in high fall risk (sensitivity, 0.73; 95% CI, 0.65–0.79) and fair accuracy for ruling out high fall risk (specificity, 0.90; 95% CI, 0.86–0.93) using a cutoff score between 45 and 50. The TUG (5 studies; N=427) had similar accuracy for ruling in high fall risk (sensitivity, 0.76; 95% CI, 0.68–0.83) but worse accuracy for ruling it out (specificity, 0.49; 95% CI, 0.68–0.83) using cutoffs of 11 to

15 seconds. Other tools analyzed also performed poorly after pooling results. The authors concluded that no individual test is sufficiently predictive for identifying elderly people at high risk of falling.

A 2013 systematic review and meta-analysis of 53 cohorts (N=12,832) investigated the ability of the TUG to detect and predict a high risk of falling in the elderly.[2] Studies enrolled people with a mean age of 75 years and living independently, mostly with follow-up periods from 6 to 12 months, but with a wide range of fall prevalence (11%–79%). To measure the TUG's discriminative ability, mean difference (MD) in test time between fallers and nonfallers was analyzed. For diagnostic accuracy, an area under the curve (AUC) was used. The AUC is a measure of how accurate a test is in classifying people as high or low risk correctly. Among seniors living independently without chronic disease, a clinically insignificant difference in test time was found (7 studies; N=1,942; MD, 0.63 seconds; 95% CI, 0.1–1.1); however, among independent seniors with mild cognitive impairment or other chronic disease, a more significant difference was found (21 studies; N=6,084; MD, 2.1 seconds; 95% CI, 1.5–2.6) in the TUG test between high- and low-risk seniors. Derived test time cut points (8 studies, N=1,899) for predicting falls ranged from 8.1 seconds (sensitivity, 83%; specificity, 61%) to 20 seconds (sensitivity, 10%; specificity, 95%). The TUG's AUC ranged widely from 0.50 to 0.89 (9 studies, N=2,204) but only two small studies (N=55) found an AUC over 0.85, the threshold indicating good accuracy. The authors concluded that the TUG is not useful in determining the risk of falling among the elderly. The study was limited by inclusion of retrospective studies, nonrandomly chosen samples, high heterogeneity, and a low number of high-quality trials.

In 2011, the American Geriatrics Society and British Geriatrics Society produced an evidence-based guideline recommending screening for fall risk in elderly persons (no strength given).[3] According to their guideline, an in-depth history and examination should be given if patients report two or more falls within the past 12 months or difficulty with walking or balance. If only one fall in 12 months is reported, the guideline recommended use of a multifactorial screening tool, such as BBS, TUG, Get Up and Go Test, or Performance-Oriented Mobility Assessment, without endorsing one specific test. EBP

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Do thiazides increase the risk of falls in the elderly?

EVIDENCE-BASED ANSWER

It depends. Diuretic usage does not increase long-term fall risk in 180 days and beyond postinitiation of treatment in the elderly (SOR: **B**, meta-analysis of cohorts, case-controls, and cross-sectional studies). However, within the first 14 to 45 days of initiation, diuretics have been associated with an increased risk of falls and fragility fractures (SOR: **C**, retrospective cohort and case series).

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A 2018 meta-analysis of 37 cohort studies, 31 case-control studies, and 11 cross-sectional studies (N=3,015,246) investigated the association between the use of antihypertensive medication classes and the risk of falls, injurious falls, or recurrent falls in older adults.[1] A subanalysis of 72 studies examining diuretic use was identified. Adults included were 60 years old or older, with most studies possessing a mean age in the 70s. The studies were split across multiple settings, including 38 in the community, 20 in mixed settings, 12 in nursing homes, and nine inpatient-based studies. Follow-up times were not directly stated, but most studies reported a follow-up time of six months or greater.

Both thiazides and loop diuretics were combined and results were given as odds ratios (ORs) for falls. Diuretics did not increase the risk of falls (38 studies, N=333,595; OR 1.1; 95% CI, 0.92–1.2), injurious falls (29 studies, N=864,225; OR 0.98; 95% CI, 0.88–1.1) or recurrent falls (8 studies, N=25,008; OR 1.2; 95% CI, 0.95–1.4) compared with nonuse. These findings were also consistent with subanalysis of patients who were 80 years old or older.

A 2015 retrospective registry-based Danish cohort study (n=1,586,554) examined the relationship of specific cardiovascular drugs and fragility fractures in elderly residents.[2] All residents of Denmark 65 years old or older over the 13-year period of 1999 to 2012 were included for analysis. Individuals were followed from study initiation, their 65th birthday, or their date of immigration to Denmark until diagnosis of a fall-related fracture, emigration, death, or the end of the study. The mean age of individuals on thiazide diuretics (n=322,262) was 75 years old. The maximum follow-up period was 14 years, with a mean follow-up of seven years. Patients treated with thiazide diuretics were significantly more likely to experience a fragility fracture compared with nonusers at 0 to 14 days postinitiation (incidence rate ratio [IRR] 1.4; 95% CI, 1.3–1.6), 15 to 30 days postinitiation (IRR 1.5; 95% CI, 1.4–1.7), 31 to 90 days postinitiation (IRR 1.3; 95% CI, 1.3–1.4), and at 91 to 180 days postinitiation (IRR 1.1; 95% CI, 1.01–1.20). The association between thiazide use and fragility fractures was strongest in the time interval of 15 to 30 days after drug initiation compared with nonuse. After 180 days of initiation, no significant difference was found in rate of fragility fractures between those on thiazides and nonusers (IRR 1.0; 95% CI, 0.97–1.0).

A 2013 population-based self-controlled case series (n=8,893) analyzed the association between the initiation of antihypertensive medications and falls in the elderly.[3] Participants were recruited from the Ontario Drug benefit Program database, and included all patients 66 years or older who experienced an injurious fall and received a first prescription from any of the following antihypertensive drugs: thiazide diuretics (n=1,344) ACE inhibitors (n=3,732), angiotensin-receptor blockers (n=290), calcium channel blockers (n=1,375), or beta-blockers (n=2,152). Patients in nursing homes or long-term care facilities were excluded from the study. Participants were examined in a 90-day pre-exposure period, a 45-day risk/study period, and a 45-day postexposure washout period. The mean age of those who suffered an injurious fall was 80 years old. A total of 1,344 patients (15.1%) were exposed to thiazide diuretics. Conditional Poisson regression was used to estimate IRRs with 95% CIs for each drug class with respect to injurious falls. Overall, an increased risk of falls was noted within 14 days (IRR 2.1; 95% CI, 1.7–2.7) and 45 days (IRR 2.1; 95% CI, 1.7–2.7) of initiation of thiazide diuretics compared with pre-exposure and postexposure control periods. EBP

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In adults with mild persistent asthma, is as-needed use of a combined inhaled corticosteroid plus long-acting beta-agonist as effective as scheduled use of an inhaled corticosteroid alone in preventing asthma exacerbations?

EVIDENCE-BASED ANSWER

Whether inhaled corticosteroid (ICS) plus long-acting beta agonist (LABA) as needed is more effective than scheduled ICS alone remains unclear (no recommendation given, conflicting data from 2 systematic reviews of randomized controlled trials [RCTs] and single RCT). However, ICS plus LABA is noninferior to scheduled use of ICS (SOR: **B**, RCT).

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A 2010 systematic review of 77 randomized controlled trials (RCTs; N=21,248) examined the safety and efficacy of addition of long-acting beta agonists (LABAs) to inhaled corticosteroid (ICS) for treatment of asthma.[1] Patients included were two years old or older, received daily ICS for at least four weeks before study entry, and were majority mild cases in severity. LABA formoterol dosed at 6 to 12 μg twice daily was used in 54% of the studies and salmeterol dosed at 50 mcg twice daily in 46% of the studies. The duration of intervention varied among studies with 43 studies (56%) lasting between 12 and 16 weeks, 16 (21%) lasting 4 to 8 weeks, and the remaining 18 (23%) lasting 24 to 54 weeks. Primary outcome measured was of the rate of asthma exacerbations requiring oral corticosteroids between groups. After pooling of 28 trials (N=6,808; 91% adults), patients on combination treatment of LABA to low-dose ICS had a significantly reduced chance of asthma exacerbations (risk ratio 0.8; 95% CI, 0.7–0.9) compared with monotherapy with a similar dose of ICS in adults.

A 2015 systematic review of five RCTs (N=2,781) examined the effects of treatment with LABA+ICS versus a step down to ICS alone for asthma patients.[2] Adults included were well controlled on maintenance LABA and ICS at any dose and then were randomly assigned to step down therapy to only ICS versus continuing on both ICS and LABA for 12 to 24 weeks. LABA options included formoterol 9 mcg twice a day or salmeterol 50 mcg twice a day. ICS regimens included budesonide 320 mcg daily (intervention) and 160 mcg twice a day (control), as well as fluticasone propionate in twice-daily dosing at 100, 250, or 500 mcg. The primary outcomes measured were differences in exacerbations requiring oral steroids, asthma control, and all-cause serious adverse events. Discontinuation of LABA did not lead to significant increases in exacerbations defined by need for oral corticosteroids (four trials, N=1,257; odds ratio [OR] 1.7; 95% CI, 0.8–3.7) or in all-cause adverse events (five trials, N=1,342; OR 0.8; 95% CI, 0.3–2.4) compared with continuing LABA.

A 2018 double-blinded RCT (n=4,215) assessed the efficacy of LABA and ICS versus maintenance ICS in controlling severe exacerbations in patients 12 years old or older with mild asthma.[3] The majority of patients included were between the ages of 18 and 64 years old. Patients were randomly assigned to either twice-daily placebo plus 200 mcg budesonide and 6 mcg formoterol of LABA and ICS (n=2,089) or as-needed ICS maintenance therapy of 200 mcg budesonide plus 0.5 mg terbutaline as needed (n=2,087). The primary outcome was the annualized rate of severe exacerbations and the difference in time to an exacerbation. No significant difference was found in annual severe exacerbations for patients in the LABA and ICS combination group compared with the ICS maintenance group (mean difference –0.01; 95% CI, –0.04 to 0.03) or for time to an exacerbation (hazard ratio 0.96; 95% CI, 0.8–1.2). EBP

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Does an asthma action plan help reduce severity of asthma exacerbations?

EVIDENCE-BASED ANSWER

Yes. Asthma action plans help improve asthma control and reduce emergency room (ER) visits compared with no written plan provided to the patient (SOR: **C**, small randomized controlled trial [RCT] and cohort). Action plans that contain pictures do not improve asthma control or quality of life but may reduce ER visits related to asthma compared with plans without pictures (SOR: **C**, small RCT).

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A 2014 randomized controlled trial (n=40) investigated pictorial asthma action plans for effectiveness in female patients with limited healthy literacy and moderate to severe asthma.[1] Patients were women 18 to 55 years old who lived in an underdeveloped region of Turkey. Excluded groups included smokers, recent respiratory infections, previous education on asthma control, and inability to give informed consent due to mental capacity. Both groups were selected in a randomized blinded manner, each receiving action plan education at one office visit, with the control group receiving the plan without the pictures. An Asthma Control Test (ACT, scored 5–25) was used with higher scores indicating better control, over 20 considered well-controlled, and a three-point difference was clinically significant. In total, 16 participants in the control group and 18 participants in the active picture group completed the study. The St. George Respiratory Questionnaire assessed health-related quality of life after six months. Multiple factors were addressed including morbidity, nonscheduled emergency room (ER) or hospital visits, health-related quality of life, and asthma control. Asthma control was better in the group with the pictorial action plan but did not retain significance after six months (ACT score 24.00 vs 23.50, $P=.069$). Health-related quality-of-life scores were lower at six months for both groups but the difference between the two groups was not significant. However, ER visits were significantly lower in the active picture group compared with the control group (0.9 vs 1.8, $P<.01$). No hospitalizations were noted for either group during the six-month time frame.

A 2018 prospective cohort (n=52) examined the efficacy of asthma action plans in children 5 to 18 years old with persistent asthma.[2] Children who had used an inhaler for the past three months and could ensure proper use were included in the study. Children with cardiovascular disease, chronic pulmonary disease, or those with asthma exacerbations that required hospitalization within a month of study onset were excluded. Forty-seven percent of children were classified with moderate persistent asthma, 31% severe persistent, and 22% of patients mild persistent based on the dosage and type of inhaled corticosteroid used. Of the children enrolled, 78% had their asthma under control, 18% had partial control, and 4% had uncontrolled asthma. Those enrolled were given an asthma action plan that composed of colorful pictures of children in different levels of discomfort along with peak flow level and symptoms of asthma. Outcomes included the number of asthma exacerbations that required ER visits, clinic visits, hospital admissions, and school absences. When compared with the absence of a written asthma action plan, six-month usage of a written asthma action plan significantly reduced ER visits (18 vs 3, $P=.006$), office visits (4 vs 0, $P=.046$), admission days (17 vs 0, $P=.026$), and school absence days (55 vs 12, $P=.022$). Limitations to the study included the following confounding variables: level of asthma control, severity of asthma, medication step up, and season. EBP

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In patients with stable COPD, is a short-acting beta agonist alone as effective for controlling symptoms as a SABA plus a short-acting muscarinic antagonist?

EVIDENCE-BASED ANSWER

In patients with COPD, it remains unclear if short-acting beta agonist alone is as effective for controlling patient-centered symptoms as combination therapy of short-acting beta agonist (SABA)+short-acting muscarinic-antagonist (SAMA) (no recommendation given from 2 systematic reviews of randomized controlled trials [RCTs]). Combination therapy of SABA+SAMA may improve post-bronchodilator testing (FEV1 and FVC) when compared with SABA monotherapy in COPD patients (SOR: **C**, inconsistent disease-oriented evidence from 2 systematic reviews of RCTs).

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A 2007 systematic review of two double-blinded RCTs (N=1,166) investigated the efficacy of SABA alone versus short-acting beta agonist plus a short-acting muscarinic antagonist (SABA+SAMA) in patients with COPD.[1] Majority of patients were men (65%) with a moderate but stable airway obstruction, a FEV1 of 65% or lower of predicted normal, a 10+ years of smoking history, and were regularly using at least two prescribed therapeutic agents for control of their COPD in the three-month period preceding the trial. Patients with a history of asthma, allergic rhinitis or atopy, with a total blood eosinophil count above 500/μL, or who required more than 10 mg of oral prednisone daily within a month before entry into the study were excluded. In the first study, researchers compared ipratropium 40 μg to ipratropium 40 μg+albuterol 120 μg delivered by metered dose inhalation at least four times per day. Patients were followed over an 85-day treatment period and assessed for improvements in FEV1 and FVC, along with changes in symptoms. After 85 days, those in the combination SABA+SAMA group had a significantly greater improvement in FVC from baseline compared to either SABA or SAMA alone (35% vs 24% or 29%, $P<.05$). No differences were noted in FEV1 improvements or any of the patient-reported symptoms between the two groups. The second trial conducted three years later was near identical in study design to the first trial summarized. Patients treated with combination SABA+SAMA did not have a significant change in FEV1 scores compared with either SAMA or SABA alone (36% vs 27% or 31%, $P>.05$). Again, all patient-measured symptoms did not differ in improvement between the monotherapy groups and the combination group.

A 2006 meta-analysis of seven RCTs (N=1,572) evaluated changes in FEV1 and FVC after treatments of SABA monotherapy or SABA+ipratropium.[2] Patients were included if possessing "stable" COPD without any history of asthma, heart, kidney or liver disease. Patient interventions included SABA treatment and ipratropium bromide+SABA combination therapy both metered dose inhalation and nebulizer, each for four-week minimum time up to eight weeks duration. After pooling of all seven trials, patients treated in the combination SABA plus SAMA group had a significant increase in FEV1 levels compared with the SABA monotherapy group (mean difference [MD] 0.07 L; 95% CI, 0.05–0.08 L) but not for FVC levels (MD 0.05 L; 95% CI, −0.21 to 0.12 L). EBP

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What is the best therapy for PCS?

EVIDENCE-BASED ANSWER

No consensus is found on the best therapy for pelvic congestion syndrome (PCS). Gonadotrophin-releasing hormone analogs, and to a lesser degree progestin agents and subdermal progesterone implants, decrease pain associated with PCS (SOR: **B**, systematic review of randomized controlled trials [RCTs]). Embolization with fibered platinum coils (FPC) has equivalent efficacy and safety as embolization with vascular plugs in improving symptomatic pain from PCS (SOR: **B**, single RCT). Gel foam and coil embolization as well as sclerosis of veins have high rates of symptom relief in treating PCS (SOR: **C**, systematic review of case series). Symptoms of PCS may relieve with use of compression shorts (SOR: **C**, small cohort).

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A 2010 systematic review (N=812) of four randomized controlled trials (RCTs) and 18 case series evaluated diagnosis and management for pelvic congestion syndrome (PCS) in women.[1] All study participants were females with pelvic pain and venous morphological distortion, though studies lacked uniform definitions and methods of diagnosis. Due to heterogenous designs of trials, data were unable to be pooled for analysis. One RCT (n=102) compared the efficacy of medroxyprogesterone (MPA), psychotherapy, placebo, or a combination of both (dosing and protocols not available). The primary outcome was at least a 50% decrease on a 0 to 10 visual analogue scale (VAS) for pain. Patients treated in the MPA with psychotherapy group had a significantly higher achievement rate compared with MPA only (71% vs 43%, $P<.05$), psychotherapy, and placebo (71% vs 53%, $P<.05$), and placebo only (71% vs 29%, $P<.05$). Another RCT (n=47) compared goserelin (3.6 mg IM/m × 4 m) and MPA 5 mg over six months of treatment. Patients in the goserelin group decreased their pelvic pain score (range 0–12) significantly lower compared with the MPA group (–7.7 vs –4.7, $P<.001$). Another RCT (n=23) compared a subcutaneous etonogestrel implant versus no therapy using 1 to 10 VAS pain scale. At 12 months, patients receiving implants had a significantly greater decrease in pain scores compared with the no treatment group (mean difference [MD] –5.3 vs –0.3, $P<.05$). Studies of percutaneous embolotherapy consistently demonstrated improvement in symptoms but none compared efficacy versus medical treatment. Studies of surgical intervention were of poor quality and had inconsistent results with some studies reporting complete resolution for all patients and others demonstrating no symptom improvement.

A 2018 RCT (n=100) sought to determine whether FPC or vascular plug embolization was more effective in relieving PCS symptoms.[2] PCS was diagnosed via doppler ultrasound and patients were excluded if they had a history of contrast reactions or any pelvic pathology issues. Half of these women with PCS (mean age 43 years old) were randomly chosen to receive FPC embolization and the other half received vascular plug embolization. Clinical success at one year was defined by relief of dyspareunia, dysmenorrhea, and urinary urgency, and also by subjective improvement of pelvic pain measured on a 0 to 10 VAS. No significant difference was found between the FPC group compared with the vascular plug group for improvement of all symptoms (90% vs 91%, $P=.76$). Of note, the FPC group had a significantly longer fluoroscopy time (33 vs 19 minutes, $P<.001$) and larger radiation doses (948 vs 320 mGy, $P<.001$) compared with the vascular plug group.

A 2018 systematic review of 14 case series studies (N=828) evaluated the efficacy of percutaneous interventions for the treatment of PCS.[3] Women included had an average age of 40 years old who underwent 994 unique percutaneous treatments for PCS and were followed for an average of 36 months. Included treatments were coil embolization (n=437), embolization with glue and lipiodized oil (n=60), sclerosant (n=33), and mixed percutaneous treatment that included sclerosant with coil and/or Gelfoam® embolization (n=196). Clinical improvement was defined as symptomatic improvement of dysmenorrhea, dyspareunia, and urinary frequency. No significant difference in clinical improvement rates was noted between coil, sclerosant, and the combined agent group (96% vs 100% vs 95%, $P>.05$). However, the glue and lipiodized oil group performed significantly worse than the other treatment groups (71% vs 95%, $P<.05$).

A 2018 cohort study (n=60) examined the effectiveness of compression stockings for treatment of chronic pelvic pain, dyspareunia, and discomfort in the hypogastrium in women with symptoms of pelvic venous congestion.[4] Class II compression shorts were used in symptomatic women without evidence of lower extremity vein pathology (n=48), and class II compression stockings were used in women with evidence

of venous insufficiency in the lower limbs (n=12). Women with asymptomatic PCS were excluded. After two weeks of daily use of the compression garments, 81% of patients in the group that used compression shorts had a significant decrease or resolution of symptoms (95% CI, 69–92%). Using a modified McGill scale ranging from severe to absent/mild pain (numerical range not specified), the severity of pelvic pain decreased from baseline (6.5 to 1.1, $P<.05$) in the group that used compression shorts. No significant improvement was noted in the severity of pelvic pain (6.3 to 6.2, $P>.05$) in the group that used compression stockings. EBP

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Is there an association between football-related head injuries and the development of depression?

EVIDENCE-BASED ANSWER

Probably. A history of concussion in professional American football players is often associated with depression later in life (SOR: **C**, systematic review of cohorts, cross-sectionals, and case studies and a single cross-sectional study).

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A 2018 systematic review of 21 observational studies examined the effect of concussions and traumatic brain injuries on cognitive, psychological, physical, and sports-related functioning in professional American football players[1]. A subgrouping of six cross-sectional studies (N=2,884), one prospective cohort (n=1,044), and two case reports (N=2) specifically examined brain injuries and their association with depression. The age of retired players ranged between 44 and 71 years, and the average mean duration of football participation was about nine years. Mild traumatic brain injury was based on self-report, diagnosis by team physician, or the use of the Sport Concussion Assessment Tool. Most studies used the Beck Depression Inventory II to measure depression, with higher scores indicating greater levels of depression. The 2012 prospective cohort (n=1,044) collected concussion frequency responses from retired National Football League (NFL) Player's Association members in 2001 and in 2010. After nine years of follow-up, a significant increase was observed in the proportion of players receiving a clinical diagnosis of depression for those with 10 or more concussions compared with those with no concussions (27% vs 3%; $P<.001$). A 2007 cross-sectional study (n=2,552) also surveyed retired NFL Player's Association members on their number of concussions, depression levels, and overall well-being. Players with a history of three or more concussions were significantly more likely to have a diagnosis of depression compared with those with none (risk ratio [RR], 3.0; 95% CI, 2.3–4.1). Another cross-sectional study (n=120) assessed cognitive and psychological functioning of players who had been on an active NFL roster for at least three years with clinical history, imaging, electroencephalogram, and had reported number of total concussions. NFL players within the sample reported a 28% incidence of

depression, compared with 9.5% in the general population. Overall, five of the nine studies examining depression found a significant link between traumatic brain injury and depression later in life.

A 2019 cross-sectional descriptive epidemiology study (n=3,506) examined whether seasons of professional football, playing position, and experience of concussions were associated with quality-of-life indicators of depression and anxiety[2]. All former players who had participated in the NFL since 1960 were mailed or emailed a questionnaire. Respondents were 53 years old on average, played seven professional seasons, began playing around 12 years old, and had three concussions over the course of playing career. The Patient Health Questionnaire-2 (PHQ-2) was used to assess symptoms of depression, which queries two depression symptoms in the past two weeks ("Little interest or pleasure in doing things" and "Feeling down, depressed or hopeless"). Players were considered to have indicators of depression if they had a score of three or greater on the PHQ-2 or current antidepressant use. Scores were then converted into an overall concussion symptom score. Compared with players with the lowest quartile concussion symptom score, players in the highest quartile had a significant increased risk for possessing indicators of depression (RR, 6.0; 95% CI, 4.7–8.7). Additionally, each five seasons of professional play was associated with a 9% increased risk of having indicators of depression, at borderline statistical significance (RR, 1.09; 95% CI, 1.00–1.18). EBP

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In patients with hyperlipidemia and cardiovascular disease, does the addition of a PCSK9 inhibitor decrease the incidence of subsequent cardiovascular events?

EVIDENCE-BASED ANSWER

PCSK9 inhibitors reduce cardiovascular death, myocardial infarction, cerebrovascular accidents, hospitalization for unstable angina, and coronary revascularization events in people with a history of cardiovascular disease (SOR: **A**, consistent results from 2 large randomized controlled trials).

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A 2018 randomized controlled trial (RCT; n=18,924) evaluated the efficacy and safety of the PCSK9 inhibitor alirocumab in patients with recent acute coronary syndrome already on statin therapy.[1] Patients were 40 years or older (75% male) and randomized to alirocumab, 75 to 150 mg every two weeks subcutaneously or placebo after being on high-intensity statin therapy (atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily) for 2 to 16 weeks. Patients younger than 40 years and experiencing an acute coronary event longer than 52 weeks prior to enrollment were excluded. Patients were followed for a median of 2.8 years and monitored for death, myocardial infarction (MI), ischemic stroke, and unstable angina. Those treated with alirocumab had moderate reductions in ischemic stroke (1.2% vs 1.6%; $P=.01$), all-cause mortality (3.5% vs 4.1%; $P=.03$), and MI (6.6% vs 7.6%; $P=.01$) compared with placebo.

A 2017 RCT (N=27,564) analyzed whether the addition of evolocumab to moderate- or high-intensity statin therapy in patients with atherosclerotic cardiovascular disease (CVD) improved patient outcomes.[2] Patients were majority white (80%) men (75%) who were randomly assigned to receive subcutaneous injections of evolocumab or subcutaneous placebo injections. Evolocumab injections were dosed at either 140 mg every two weeks or 420 mg monthly. The participants all had CVD (defined as a history of MI, nonhemorrhagic stroke, or symptomatic peripheral artery disease) with 80% also having hypertension, 37% having type 2 diabetes, and 28% using tobacco products. Major exclusion criteria included MI or stroke within the prior four weeks, advanced heart failure, uncontrolled ventricular tachycardia, and chronic kidney disease. More than 99% of the patients were concurrently using moderate- to high-intensity statin therapy (at least atorvastatin 20 mg daily or its equivalent, with or without ezetimibe). Almost all patients were taking antiplatelet therapy, 76% were taking beta-blockers, and 78% were taking an ACE inhibitor or angiotensin receptor blockers at trial entry. Patients were followed for a median duration of 26 months. Compared with the placebo group, the evolocumab group had a significantly lower risk of the composite outcome of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization (hazard ratio [HR], 0.85; 95% CI, 0.79–0.92). Those in the treatment group also experienced a reduction in the key secondary end point of cardiovascular death, MI, or stroke compared with placebo (HR, 0.80; 95% CI, 0.73–0.88). EBP

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How effective is metformin in reducing cardiovascular risks in adults with T2DM?

EVIDENCE-BASED ANSWER

Metformin is not superior in reducing cardiovascular risks compared with other preventative treatments such as diet and lifestyle in adults with type 2 diabetes mellitus (SOR: **A**, 2 meta-analyses of randomized controlled trials [RCTs]). However, metformin reduces cardiovascular events about 20% more than placebo or no treatment (SOR: **A**, meta-analysis of RCTs).

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A 2017 meta-analysis of 13 RCTs (N=4,233) evaluated the effects of metformin on cardiovascular outcomes compared with diet, lifestyle, and placebo.[1] Patients had type 2 diabetes, an average age between 53 and 65 years, average baseline body mass index ranging from 29 to 34 kg/m^2, and an average HbA1c of 6.9% to 9.1%. Of the pooled patients from the 13 trials, 2,079 were allocated to the metformin intervention group and the remainder were allocated to either no intervention/placebo (11 trials) or a lifestyle modification (2 trials). Metformin dosages were not explicitly stated but described as "standard." Outcomes were reported as risk ratios [RRs] and measured risk of all-cause mortality, cardiovascular death, myocardial infarction (MI), stroke, and peripheral vascular disease over an average period of two years (6 months to 18 years). When compared with control groups, metformin therapy was not significantly different in rates for all-cause mortality (13 trials, N=4,156; RR, 0.96; 95% CI, 0.84–1.1), cardiovascular death (12 trials, N=3,785; RR, 0.97; 95% CI, 0.80–1.2), MI (7 trials, N=2,502; RR, 0.89; 95% CI, 0.75–1.1), stroke (4 trials, N=2,051; RR, 1.04; 95% CI, 0.73–1.5) and peripheral vascular disease (4 trials, N=2,051; RR, 0.81; 95% CI, 0.50–1.3). Adverse events were not specified. Limitations included a majority of patients on comedications and a lack of minority populations.

A 2011 meta-analysis of 12 RCTs (N=14,451) examined the efficacy of metformin on reducing the

incidence of cardiovascular events and mortality.[2] Patients were mostly diagnosed with type 2 diabetes (10 trials, N=11,770), had mean ages of 45 to 67 years old, and average HbA1c values of 5.9% to 12%. Patients were randomized to either receive metformin (N=5,455) from 43 to 3,000 mg daily or to no therapy, placebo, and active glucose-lowering therapies (N=8,996). The trial lengths had a median duration of 2.2 years with a range of 1 to 11 years in total. Primary outcomes were the number of cardiovascular events defined as MI, stroke, peripheral artery disease, or cardiovascular death. Other outcomes measured were the all-cause mortality and incidence of heart failure. Compared with all control groups, metformin did not significantly reduce cardiovascular events (12 trials, N=14,451; odds ratio [OR], 0.94; 95% CI, 0.82–1.1). But separate analyses did demonstrate a significant reduction in cardiovascular events with metformin in comparisons with placebo or no therapy (8 trials, N=4,501; OR, 0.79; 95% CI, 0.64–0.98) but not in active comparator trials of thiazolidinediones (three trials, n=6,329; OR, 1.0; 95% CI, 0.83–1.2) or other glucose-lowering medications (3 trials, N=4,238; OR, 1.1; 95% CI, 0.54–2.1). Further statistical analysis showed that metformin did not appear to have any effect on all-cause mortality when comparing all comparators, but it did significantly increase mortality in two studies where metformin was added to sulfonylureas. Adverse events were not specified. A limitation of the meta-analysis was the lack of race or ethnicity data of patients in the studies. EBP

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Does starting a beta-blocker in the preoperative period decrease perioperative mortality and morbidity?

EVIDENCE-BASED ANSWER

For cardiac procedures, perioperative beta-blockers decrease arrhythmias by 63% but do not affect mortality. For noncardiac procedures, they decrease both myocardial infarction and supraventricular tachycardia, but increase mortality, hypotension, bradycardia, and strokes (SOR: **A**, systematic review and meta-analysis). In noncardiac vascular and endovascular surgeries, they do not affect morbidity or mortality (SOR: **A**, systematic review and meta-analysis).

DOI 10.1097/EBP.0000000000001305

A 2018 systematic review (88 randomized controlled trials [RCTs], N=19,161) analyzed the effects of perioperatively administered beta-blockers for prevention of surgery-related morbidity and mortality.[1] The trials included adults undergoing any surgery under general anesthesia. The authors divided the results by cardiac and noncardiac procedures. Any beta-blocker dose or route could be used as the intervention and were initiated before surgery, during surgery, or by the end of the first postoperative day. The control group was either placebo or standard care. The primary outcome was all-cause mortality occurring within 30 days of surgery or before hospital discharge. Secondary outcomes included cardiac mortality and events, bradycardia, and hypotension. Among patients undergoing cardiac surgeries, perioperative beta-blockers decreased risk of ventricular arrhythmias (12 trials; N=2,292; risk ratio [RR] 0.37; 95% CI, 0.24–0.58; number needed to treat [NNT]=29) and supraventricular tachycardia (48 trials; N=6,420; RR 0.44; 95% CI, 0.36–0.53; NNT=5). No significant differences were found for all-cause

mortality, myocardial infarction, cerebrovascular events, hypotension, bradycardia, or congestive heart failure (CHF). In the noncardiac surgery group, beta-blockers decreased risk of myocardial infarction (14 trials; N=10,958; RR 0.73; 95% CI, 0.61–0.87) and supraventricular tachycardia (8 trials; N=8,744; RR 0.73; 95% CI, 0.57–0.94), but they increased risk of all-cause mortality (13 trials; N=11,413; RR 1.3; 95% CI, 1.0–16), hypotension (21 trials; N=10,947; RR 1.5; 95% CI, 1.4–1.6), bradycardia (23 trials; N=11,033; RR 2.2; 95% CI, 1.5–3.4), and strokes (5 trials; N=9,150; RR 1.6; 95% CI, 0.93–2.7). Beta-blockers had no significant effect on ventricular arrhythmias or CHF. Limitations included a risk of bias in some studies because of inclusion of patients not undergoing general anesthesia.

A 2017 systematic review and meta-analysis (3 RCTs, 8 cohort studies, N=32,602) investigated the effect of preoperative beta-blocker use in noncardiac vascular and endovascular surgery on all-cause mortality.[2] Two of the RCTs overlapped with the above 2018 systematic review. Patients were included if they had an elective vascular or endovascular surgery and were more than 18 years old. Treatment included any beta-blocker of any dose, titration, duration, or mode of administration. The intervention group was compared with placebo or no treatment. The primary outcome measured was all-cause mortality, and the follow-up period ranged from 30 days to 84 months. Secondary outcomes included cardiac mortality and events, renal failure, rehospitalization, and reoperation. No significant difference was found between the treatment and control groups for all-cause mortality (7 studies; N=14,352; OR 1.1; 95% CI, 0.59–2.0) or cardiac mortality (4 studies; N=2,406; OR 2.6; 95% CI, 0.86–8.1); significant differences were also not found for the outcomes of myocardial infarction, unstable angina, stroke, arrhythmias, CHF, other cardiovascular events, renal failure, or reoperation. Limitations included the inability to exclude reporting bias. EBP

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Does potassium supplementation improve hypertension control?

EVIDENCE-BASED ANSWER

Potassium supplementation has been associated with 4 to 8 mmHg decreases in systolic blood pressure (SBP) and 3 to 6 mmHg decreases in diastolic blood pressure (DBP) among patients diagnosed with essential hypertension (SOR: **C**, disease-oriented evidence from a meta-analysis of randomized controlled trials [RCTs] and a single RCT).

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A 2017 meta-analysis of 23 RCTs (N=1,213) studied the effect of potassium supplementation compared with either placebo or no treatment on SBP and DBP in patients with primary hypertension.[1] Primary hypertension was defined as a resting SBP of more than 140 mmHg and a DBP of greater than 90 mmHg. Normotensive patients and those with secondary hypertension were exclusion criteria, and some trials excluded those with coronary artery disease, dyslipidemia, myocardial abnormalities, and diabetes. Potassium was supplemented with a median of 64 mmol/d (range, 6–200 mmol/d), and follow-up was for a median of four weeks (range, 4–52 weeks). One trial was excluded from pooled analysis as an extreme outlier prone to bias. Twenty-two studies were pooled for analysis and indicated that potassium supplementation significantly reduced SBP (mean difference [MD], −4.3 mmHg, 95% CI, −6.0 to −2.5 mmHg; I^2=41%) and DBP (MD −2.5 mmHg, 95% CI, −4.1 to −1.0 mmHg; I^2=65%), compared with placebo/control groups. Subgroup analysis was performed

between the continents where the studies were conducted and by stratified potassium dosing (<50, 50–99, >100 mmol daily). The continent subgroup analysis did not reveal any significant differences between America, Europe, Asia, and Australia ($\chi^2 = -1.7$; $P = .63$). The analyses by potassium supplement dose suggested a dose-response relationship; however no statistical analysis was performed to confirm the significance of this relationship.

A 2005 RCT (N=104), the individual trial of highest quality included in the above meta-analysis, compared potassium supplementation with no treatment for hypertension treatment.[2] Patients were majority male, 35 to 66 years old, and diagnosed with hypertension defined as a SBP of greater than 140 mmHg and a DBP greater than 90 mmHg. Any patients with a SBP of greater than 200 mmHg, any diagnosed cardiac issue, or those with diabetes were excluded. Patients were randomized into two groups of 52 patients each to receive four weeks of 30 mmol/d potassium (liquid in a premeasured vial) daily or no treatment. Compared with baseline readings, the potassium supplementation significantly lowered BP levels at both SBP (MD −12.3 mmHg; $P<.001$) and DBP (−7.8 mmHg; $P<.001$) after four weeks of treatment. Additionally, 24-hours ambulatory monitoring indicated that potassium supplementation reduced mean 24-hour SBP (−7.9 mmHg; $P<.001$; 142.7 versus 134.8; $P<.001$) and DBP (−6.2 mmHg, $P<.001$). No difference was noted in the untreated group for either comparison. EBP

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In patients with *Clostridium difficile* infection, is fecal microbiota transplant better than vancomycin for resolving diarrhea?

EVIDENCE-BASED ANSWER

Probably. In patients with recurrent or refractory *Clostridium difficile* infection (CDI), fecal microbiota transplantation (FMT) via nasogastric tube or colonoscope after pretreatment with vancomycin (FMT-V) is likely superior to vancomycin alone in resolving diarrhea (SOR: **C**, mixed evidence from systematic review of randomized controlled trials [RCTs] and two single RCTs). We found no literature addressing FMT to treat primary CDI, and more research is needed for this determination.

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A 2017 systematic review of 10 randomized controlled trials (RCTs) (N=657) compared the rate of *Clostridium difficile* infection (CDI) recurrence among patients who received fecal microbiota transplantation with vancomycin (FMT-V), antibiotic therapy, autologous stool transplantation, or placebo.[1] A subanalysis of two highly homogenous RCTs (N=81) comparing vancomycin alone with FMT-V was identified. Patients included were from the Netherlands and Italy with recurrent CDI after at least one prior episode that was adequately treated with antibiotics. One trial (n=42) compared a two-week course of 500 mg of oral vancomycin four times daily with or without bowel lavage on day four or five to a four-day course of oral vancomycin 500 mg four times a day followed by bowel lavage and FMT via nasogastric tube. The second study (n=39) measured recurrence rates for patients who received a shortened three-day regimen of oral vancomycin 125 mg four times a day followed by one or

more FMTs via colonoscopy. The control group received a standard regimen of oral vancomycin 125 mg four times daily for 10 days followed by 125 to 500 mg every two to three days for at least three weeks. The measured outcome for both studies was recurrence of infection within 10 weeks. Pooled data analysis of both trials showed the FMT-V group had a significantly reduced risk of relapse when compared with the vancomycin-only group (risk ratio [RR] 0.20; 95% CI, 0.09–0.46). Limitations included small sizes and narrow demographic selection of participants.

A 2019 single-center RCT (n=64) of Danish adults compared FMT-V with vancomycin alone for recurrent CDI.[2] Adults who were enrolled were admitted for a recurrent CDI confirmed by PCR and had previously been treated at least once with vancomycin or fidaxomicin. Patients were excluded if critically ill, pregnant, or if the treating physician determined that the patient would not tolerate randomization. Participants were randomized to receive 4 to 10 days of oral vancomycin 125 mg four times daily followed by FMT via nasogastric tube or colonoscopy (n=24), or oral vancomycin 125 mg four times daily alone for 10 days (n=16). The primary outcome measured was clinical resolution and a negative *C. difficile* toxin PCR eight weeks postrandomization. The proportion of patients who experienced clinical resolution of symptoms was significantly greater in the group receiving FMT-V compared with the vancomycin-only group (71% vs 19%, *P*=.001). Limitations included small sample size, narrow inclusion criteria, and unblinded interventions.

A 2017 RCT of Canadian adults (N=30) experiencing recurrent CDI compared treatment with FMT via enema to oral vancomycin taper.[3] Included were immunocompetent adult patients with at least two episodes of laboratory confirmed CDI. Patients were excluded if critically ill, pregnant, or if they had a bleeding disorder. Participants were randomized into treatment with a 14-day course of oral vancomycin 125 mg four times daily followed by FMT via enema (n=16) or a six-week course of oral vancomycin taper: 125 mg four times daily for 14 days, then twice daily, once daily, every second day, and every third day, each for a week (n=14). The primary outcome measured was recurrence of clinically significant CDI within 120 days. The trial initially planned to include 57 patients; however, it was stopped when interim futility analysis showed no significant difference recurrence for the vancomycin-only group compared with the FMT plus vancomycin group (RR 1.4; 95% CI, 0.61–3.0). Limitations again included a small sample size, unblinded interventions, and the demographic homogeneity. EBP

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In children with atopic dermatitis, does topical bleach as adjunct therapy result in improved pruritus and fewer skin lesions as compared with traditional therapy alone?

EVIDENCE-BASED ANSWER

No. Dilute bleach baths as adjunct therapy do not relieve pruritus or area and intensity of lesions in children with atopic dermatitis compared with normal water baths (SOR: **A**, systematic review of randomized controlled trials [RCTs] and single RCT).

DOI 10.1097/EBP.0000000000001231

A 2017 systematic review and meta-analysis of four randomized controlled trials (RCTs; n=116) examined the effectiveness of bleach baths in reducing severity of atopic dermatitis.[1] Patients (3 months to 12 years old) had moderate-to-severe atopic dermatitis by Hanafin and Rajka criteria, or modifications of the same scale. Treatments lasted between 5 to 10 minutes long with solutions of 0.006% bleach and one trial using a cleanser containing bleach. Children in control groups were bathed in regular water baths. Children bathed twice a week in most trials, and all studies used baths as adjuncts to stable emollient regimens. Improvement was defined as reductions in the mean body surface area (BSA) involved or decrease in Eczema Area and Severity Index (EASI) scores. Both scoring systems evaluate the total area of the skin affected by dermatitis as a percentage of the body covered. Studies assessed severity of atopic dermatitis at intervals ranging from 2 to 12 weeks. After all four trials were pooled, children treated in the bleach bath groups had no significant reduction compared with the water bath group for both EASI score (–11% vs –14%, *P*=.16) and the BSA score (–43% vs –41%, *P*=.36) at four weeks.

A 2016 RCT (n=40) assessed the effect of bleach baths on *Staphylococcus aureus* skin colonization in children with moderate-to-severe atopic dermatitis from Hong Kong.[2] Children and adolescents between four and 18 years old with moderate-to-severe atopic dermatitis were recruited from an outpatient clinic at a Hong Kong university teaching hospital. Patients were excluded for evidence of cutaneous infection, recent treatment with oral antibiotics, or sensitivity to pool water. Participants were provided with tubs and bottles of either 0.005% bleach (n=20) or water (n=20) and instructed to bathe for 10 minutes 2 to 3 times weekly. Participants were instructed to empty the bottles underwater to maintain study blinding. Evaluations took place after four weeks of treatment, followed by a four-week washout period, then four weeks of crossover treatment. Pruritus was quantified on a 0 to 10 scale, with lower numbers indicating less pruritus. Lesion area was reported as percent BSA involved. No significant benefit was noted in bleach treatments over water in pruritus intensity (–0.18 vs –0.80, *P*=.16). Water baths resulted in a significant reduction in overall affected areas compared with the bleach baths (–5.8% vs +2.2%, *P*=.04). EBP

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Does vitamin D supplementation help with weight loss and BMI?

EVIDENCE-BASED ANSWER

Vitamin D supplementation with or without calcium does not improve weight loss in obese or overweight individuals compared with placebo (SOR: **A**, 2 meta-analyses of randomized controlled trials). The effect of vitamin D supplementation on body mass index remains unclear.

DOI 10.1097/EBP.0000000000001294

A 2019 systematic review and meta-analysis of 11 double-blinded randomized controlled trials (RCTs) examined the effectiveness of cholecalciferol supplementation

on weight loss in overweight and obese individuals.[1] Patients included were mostly women (83%) and had a body mass index (BMI) of at least 25 kg/m^2 with no restrictions of other comorbidities. Dosing of the supplementation varied greatly between trials from 25,000 to 600,000 IU/mo, but most trials dosed cholecalciferol around 2,000 IU/d. All trials included compared cholecalciferol with a nonsupplementation, with some trials also including low-calorie diets, exercise programs, and calcium supplementation as well. Total treatment time ranged from 1 to 12 months with a mean duration of five months. Compared with the control groups, the cholecalciferol dosing group experienced no significant overall weight loss (11 trials, N=947, mean difference [MD] –0.43 kg; 95% CI, –1.1 to 0.19 kg). However, supplementation did lower BMI (5 trials, N=642, MD –0.32 kg/m^2; 95% CI, –0.52 to –0.12 kg/m^2) and waist circumference (4 trials, N=592, MD –1.4 cm; 95% CI, –2.4 to –0.42 cm) compared with controls.

A 2013 meta-analysis of nine RCTs (N=1,651) analyzed the effects of 25[OH]D supplementation on BMI change in adults.[2] Initial BMI of participants ranged from 26 to 35 kg/m^2 with a mean BMI around 30 kg/m^2. Patients were 83% women and had a mean age of 48 years old. The 25[OH]D supplementation ranged from 200 to 1,110 IU daily, with the majority being between 200 and 400 IU/d. Duration of treatment ranged from 6 to 196 weeks with a median duration of 22 weeks. Also, of note, five of the included trials (N=1,235) included calcium supplementation as well in both groups. After pooling all nine trials, no significant change was noted in BMI between the 25[OH]D supplementation group and control groups (MD –0.01 kg/m^2; 95% CI, –0.11 to 0.09 kg/m^2). No other secondary outcomes were evaluated. Some limitations of this analysis include the large percent of females, the coadministration of calcium in some studies, the small number of study subjects, and the variation in doses of 25[OH]D. EBP

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Does social media use adversely affect sleep duration in adults?

EVIDENCE-BASED ANSWER

Most likely. Social media use near bedtime for up to an hour or more is associated with shortened sleep duration, increased sleep disturbance, and poor quality sleep in subjects who use social media often. (SOR: **B**, consistent findings from 2 large, cross-sectional, cohort studies.)

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A 2017 cross-sectional study (n=855) measured the relationship between in-bed electronic social media use and differing sleep quality factors.[1] Participants were hospital employees and university students from a single academic US hospital (mean age of 44 years and 85% female). Insomnia, daytime sleepiness, anxiety, and depression were measured via the minimal insomnia severity scale, Epworth sleepiness scale, and public health questionnaire for depression and anxiety, respectively. Participants were asked how many nights a week on average they used their mobile phone for electronic social media use in the hour before they went to bed and in bed. Social media use was recorded as an electronic social media (ESM) score. The ESM score represented the number of nights per week a participant used social media in bed multiplied by the time of said use. Use under a half hour was multiplied by one, one half hour to hour was multiplied by two, 1 to 2 hours by three, 2 to 3 by four, and greater than three hours by five. Scores of zero represented no in-bed use (n=269), scores of 1 to 10 represented low in-bed use (n=349), and scores of 11 or higher represented high use (n=237). When compared with survey participants with no in-bed social media use, participants with high use were significantly more likely to report symptoms of insomnia (odds ratio [OR], 2.3; 95% CI, 1.5–3.5),

anxiety (OR, 1.7; 95% CI, 1.1–2.7), and significantly less likely to sleep more than six hours (OR, 0.55; 95% CI, 0.39–0.83). No difference was observed in daytime sleepiness between the groups.

Another 2017 cross-sectional study (n=1,763) surveyed US adults 19 to 32 years old to assess the relationship between social media use and sleep disturbance.[2] Survey participants were asked how often they checked social media the 30 minutes prior to bed, with 42% indicating that they rarely did, 26% indicating that they sometimes did, and 32% checking often or very often. Sleep disturbance was assessed using the Patient-Reported Outcomes Measurement Information System sleep disturbance scale, which includes frequency of problems with sleep, difficulty falling asleep, whether sleep was refreshing and sleep quality over the past seven days. The four items included here were rated on a Likert scale, ranging from not at all (1) to very much (5), where low sleep disturbance corresponded to raw scores of 4 to 8, medium corresponded to raw scores of 9 to 11, and high corresponded to raw scores of 12 to 20. To control for cofounding variables, the outcomes were adjusted by demographic information, socioeconomic status, and relationship status. Adults who often or very often checked social media before bedtime had increased sleep disturbance compared with adults who rarely or very rarely checked (adjusted OR [aOR], 1.6; 95% CI, 1.3–2.3). Additionally, those who sometimes checked social media before bed were also significantly more likely to have increased sleep disturbance compared with the rarely check group (aOR, 1.5; 95% CI, 1.1–2.1). The authors indicated that this increase in both groups suggested a linear trend associated with use. EBP

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Is intra-articular saline injection effective for the treatment of osteoarthritis?

EVIDENCE-BASED ANSWER

It is unclear. In patients with osteoarthritis of the knee, intra-articular (IA) saline injections may provide improved pain scores from three months up to two years compared with baseline in studies where IA saline was intended as a placebo control (SOR: **B**, based on consistent findings from two systematic reviews and meta-analyses and a single randomized controlled trial [RCT]). IA saline appears to be about as effective as steroid injections and may better preserve knee cartilage (SOR: **B**, single RCT).

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A 2016 systematic review and meta-analysis of 13 randomized controlled trials (RCTs; N=1,076) evaluated the efficacy of various intra-articular (IA) injections versus saline injections for knee osteoarthritis.[1] Patients (mean age 63 years old, 64% female) had a mean body mass index of 29 kg/m^2 and a severity of osteoarthritis between one and four on the Kellgren–Lawrence (K-L) grading system, with 50% included at the highest level. A sub-analysis of three trials (N=210) was identified that contained enough valid data to analyze total Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores and a 0 to 100 visual analog scale (VAS) for pain preinjection and postinjection at three and six months. The WOMAC pain scale is based on a self-administered questionnaire consisting of 24 items in three subscales (Pain, Stiffness, and Physical Function) rated from none (0) to extreme (4) pain. IA saline injection was associated with a slight improvement in VAS scores at three months compared with baseline (3 trials, N=210;

mean difference [MD] –12.0; 95% CI, –3.0 to –20). There was no significant improvement in pain measured by the WOMAC at three months of IA saline compared with baseline (2 trials, N=180; MD –20; 95% CI, 0.5 to –40). At six months after injection, patients receiving IA saline injections experienced significantly and clinically relevant improvements in the VAS pain scale (2 trials, N=180; MD –17; 95% CI, –12 to –21) and the WOMAC (2 trials, N=180; MD –11; 95% CI, –7 to –15). No serious adverse events were reported, and one study reported two local postinjection reactions.

A 2014 systematic review and meta-analysis of 38 RCTs (N=2,589) assessed the clinical benefit associated with IA saline injections used as placebo in trials of various IA therapies for patients with painful knee osteoarthritis.[2] Diagnosis was defined by the American College of Rheumatology criteria, confirmed by the radiographic K-L score, Ahlback classification, Larsen score, or other knee osteoarthritis diagnostic criteria. The mean age of participants was 64 years old and 64% were female. Because of the variation in pain measurement scales used in trials, scores were pooled and converted into a standardized mean difference (SMD) from baseline to short term (up to 3 months or less) and long term (6 to 12 months). Pooling of 32 RCTs (N=1,705) demonstrated a significant, moderate short-term benefit in knee pain from baseline (SMD –0.68; 95% CI, –0.8 to –0.6, I^2=50%), and 19 RCTs (N=1,445) showed long-term improvement in knee pain from baseline (SMD –0.61; 95% CI, –0.76 to –0.45, I^2=74%) in patients receiving saline IA injections. Adverse events, such as local skin reactions, were reported in 29 trials. However, none of them were serious.

A 2017 RCT of 140 patients with symptomatic knee osteoarthritis (K-L grade 2–3) and ultrasound evidence of synovitis compared the effects of IA injections of triamcinolone and saline.[3] Patients included were older than 45 years old, with diagnosed knee osteoarthritis by the American College of Rheumatology classification criteria, and a WOMAC pain score between two and eight. Exclusion criteria included diagnoses of inflammatory joint disease, recent IA or hyaluronic acid injections, or a contraindication to magnetic resonance imaging (MRI) use. Primary outcomes were quantitative cartilage volume measured by MRI annually and quality of life measured by WOMAC pain scores every three months. Patients who received IA triamcinolone had a greater amount of cartilage loss at two years than those in the saline arm (MD –0.21 mm; 95% CI, –0.20 mm to –0.03 mm) though volume of clinically significant cartilage loss was undetermined. No significant difference in WOMAC pain scores was noted between the two groups at 12 months (MD –0.06; 95% CI, –1.6 to 0.3). There was no significant difference in adverse events in the two groups. The authors concluded that IA saline provided comparable pain relief without the accelerated cartilage loss associated with triamcinolone. Limitations of the study included no "sham" injection and measurements of pain at three-month intervals, thus limiting conclusions about short-term benefits. EBP

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For patients hospitalized with bone/joint infections, are oral antibiotics an effective alternative to continued IV therapy after hospital discharge?

EVIDENCE-BASED ANSWER

Oral antimicrobial therapy is noninferior to intravenous (IV) antibiotic therapy for complex orthopedic infections after hospital discharge (SOR: **B**, single randomized control trial [RCT]). There is no difference between oral and IV antibiotics for resolution of osteomyelitis symptoms following surgical debridement (SOR: **B**, systematic review of small RCTs with limitations).

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A 2019 multicenter, open-label, randomized, noninferiority trial in the United Kingdom compared organism-directed intravenous (IV) and oral antibiotic therapy after hospital discharge for complex orthopedic infections requiring at least six weeks of treatment (N=1,054).[1] The most common diagnoses included metalware-related infections (60.6%) followed by chronic osteomyelitis (35.6%), diskitis, spinal osteomyelitis, and epidural abscess. Infection was considered definitive in 90.5% of cases, probable in 2.2%, and possible in 7.2%. Patients received either definitive surgical intervention (92% of patients) or directed IV antibiotic therapy within the first seven days of hospitalization. Patients with less than one-year life expectancy, *Staphylococcus aureus* bacteremia, endocarditis, septic shock, nonbacterial orthopedic infections, infections with no oral therapy options, or infections requiring less than six weeks of therapy were excluded. Patients continued oral antibiotics after the treatment period if clinically indicated. The noninferiority margin was set at 7.5% prior to data analysis. The primary outcome was definitive treatment failure one year after randomization, defined as having a draining sinus tract, presence of frank pus, bacteria isolated from two or more deep tissue samples, aspirate, or local biopsy. Follow-up data were missing for 39 patients. Using intention-to-treat analysis, treatment failure at one year occurred in 14.6% of the IV antibiotic group compared with 13.2% in the oral antibiotic group (risk difference, –1.4%; 95% CI, –5.6% to 2.9%).

A 2013 systematic review evaluated antibiotic treatment following surgical debridement for chronic osteomyelitis (8 small, randomized, clinical trials; N=282).[2] Patients were mostly adult men with posttraumatic osteomyelitis typically affecting the tibia and femur. Trials included variable antibiotic regimens, length of treatment, and lack of predefined follow-up periods. All studies were considered at moderate-to-high risk of bias because of the lack of allocation concealment. It is unclear in four trials if all patients underwent surgical debridement. In a subset of trials assessing the oral antibiotic therapy compared with IV organism-directed therapy after hospital discharge, no statistically significant differences were found in resolution of all osteomyelitis signs and symptoms at the end of treatment protocol (4 trials, N=150, risk ratio [RR], 1.04; 95% CI, 0.92–1.18) or after one year (3 trials, N=118, RR, 0.94; 95% CI, 0.78–1.13). EBP

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In adults with AWS does phenobarbital reduce hospital length of stay more than benzodiazepines?

EVIDENCE-BASED ANSWER

It is unclear. There is conflicting evidence regarding reduction in hospital length of stay for severe alcohol withdrawal syndrome treated with phenobarbital compared with benzodiazepines (No recommendation given). Combination intravenous (IV) phenobarbital and IV lorazepam may be superior to IV phenobarbital or IV diazepam alone (SOR: **B**, single cohort).

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A 2017 retrospective cohort study (n=120) compared a novel phenobarbital protocol with the standard Clinical Institute Withdrawal Assessment of

Alcohol (CIWA-Ar)–based lorazepam protocol for the treatment of alcohol withdrawal syndrome (AWS) in an intensive care unit (ICU) setting.[1] Patients were almost exclusively white, majority male with a mean age of 50 years. The two different treatment groups had similar comorbid conditions, including psychiatric disorders, history of delirium tremens, polysubstance abuse, and liver disease. All cases that met criteria through a retrospective chart review of ICU patients were admitted over one years' time were included in the analysis. An equal number of patients received the standard of care CIWA-Ar protocol with lorazepam and the new protocol initiated in 2017 with phenobarbital. The phenobarbital protocol was based on the risk of progression to or active signs of AWS with a loading dose range of 64.8 mg orally three times a day to one dose of 260 mg intravenous (IV), with taper. The CIWA-Ar–based protocol used an initial lorazepam loading dose of 1 to 6 mg IV, followed by an IV infusion or subsequent bolus dosing, based on CIWA-Ar scores. The phenobarbital protocol group had a significantly shorter hospital length of stay compared with the lorazepam group (4.3 vs 6.9 days; $P=.004$).

A 2019 retrospective cohort study (n=562) examined the effectiveness of phenobarbital for the management of AWS compared with lorazepam.[2] All adult (mean age, 49 years; 81% male) patients admitted to a large general hospital over a 4-year period who received pharmacologic treatment for AWS with phenobarbital (n=143) or lorazepam (n=419) were included. The comparison groups were significantly different in some baseline characteristics. The phenobarbital group had a higher prior history of AWS (91% vs 73%; $P<.001$), history of seizure (73% vs 45%; $P<.001$), history of alcohol withdrawal delirium (38% vs 26%; $P<.001$), and current seizure prior to admission/arrival in emergency department (ED) (14% vs 7%; $P<.001$) compared with the lorazepam group. Phenobarbital was administered in a loading dose of 15 mg/kg in three intramuscular injections followed by oral therapy with the dose tapered by 50% every 48 hours. Lorazepam was administered in a standing dose pathway withhold parameters (median dose 13 mg on day 1 decreasing to median dose 9 mg by day 3). No significant difference was found in patient length of stay between the phenobarbital and benzodiazepine groups (5.3 days vs 5.1 days; $P=.73$). This study was limited by the potential confounder of differences between the groups that might affect the length of stay.

A 2017 single-center, retrospective, observational, cohort study (n=300) examined the effectiveness and safety of three different hospital institutional protocols during three separate periods using benzodiazepines and barbiturates for the treatment of AWS in the emergency room.[3] Adults (average age, 47 years; 77% male) requiring emergency department treatment for AWS and receiving at least one dose of protocol-based treatment per their Severity of Ethanol Withdrawal Symptoms Score were included. Pregnant and incarcerated patients were excluded. Convenience samples of 100 patients each were obtained from a protocol treatment of IV diazepam, combination IV lorazepam and IV phenobarbital, and only IV phenobarbital. Dosing in groups varied based on the patient's severity of alcohol withdrawal. Lorazepam was dosed at 2 to 4 mg IV, with phenobarbital dosed at 65 to 650 mg IV, and dosing of diazepam was not reported. The primary outcome was the rate of ICU admission from the ED; however, one of the secondary outcomes was the total length of hospital stay. No difference was observed in the rate of ICU admissions when compared against all three treatment groups. This remained true for individual comparison between any two groups. The protocol using a combination of IV lorazepam and IV phenobarbital resulted in a significantly lower total hospital stay length compared with IV diazepam or IV phenobarbital alone (51 h vs 59 h vs 70 h; $P=.04$). EBP

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In adult patient with stroke, does treatment with a statin reduce morbidity and mortality compared to placebo or no treatment?

EVIDENCE-BASED ANSWER

Statin therapy significantly reduces ischemic stroke and cardiovascular events but does not decrease all-cause mortality (SOR: **A**, meta-analysis of RCTs). A linear relationship between LDL cholesterol and absolute risk reduction for recurrent stroke underlines statin benefit (SOR: **A**, meta-analysis of RCTs).

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A 2019 meta-analysis of nine RCTs (N=10,471) examined the effectiveness of statins for secondary prevention in patients with nonhemorrhagic stroke or transient ischemic attack (TIA).[1] Patients (mean age ~68 years old) were recruited from nursing homes, hospitals, and ambulatory clinics and received a daily statin or placebo. Multiple types of statin (in increasing order of prevalence, rosuvastatin, pravastatin, simvastatin, and atorvastatin) and various dosages were used. Of the dosages, one out of 10 trials investigated statins at a low-intensity dose, seven at a moderate-intensity dose and two at a high-intensity dose. Primary outcomes measured were all-cause mortality and stroke (ischemic or hemorrhagic) and average follow-up time was 2.5 years. Statin use did not significantly reduce subsequent strokes (ischemic and hemorrhagic) compared with placebo (7 trials, N=10,398; odds ratio [OR] 0.90; 95% CI, 0.80–1.02) but did significantly reduce ischemic stroke alone (8 trials, N=10,394; OR 0.81; 95% CI, 0.70–0.93). An increase in hemorrhagic strokes was noted (6 trials, N=9,976; OR 1.54; 95% CI, 1.1–2.2), but this was sensitive to one large trial, and when excluded, no difference was seen (OR 1.4; 95% CI, 0.78–2.3). No reduction in all-cause mortality was noted between groups (5 trials, N=6,910; OR 1.0; 95% CI, 0.87–1.3). The statin group did have significantly lower rates of cardiovascular events compared with those on placebo (6 trials, N=10,192; OR 0.75; 95% CI, 0.69–0.83). Side effects, including myalgias and elevated CK levels, were not significantly different between groups. Limitations included inconsistencies in medications and dosage, study structure, and diagnostic imprecision among the studies included.

Another 2019 meta-analysis of eight RCTs (N=73,400) studied the effects of statins in ischemic stroke patients in both primary and secondary prevention trials.[2] A subanalysis of four secondary prevention trials (N=10,200), each including at least 500 stroke patients and excluding specific subgroups of stroke patients (ie, only stroke with hemodialysis) was identified. The intervention arm received standard doses (not exactly specified) of simvastatin, pravastatin, atorvastatin, and simvastatin plus ezetimibe to an average LDL range from 53 to 104 mg/dL. Patients were treated and followed for an average of 5 to 6 years. After pooling the four secondary prevention trials, patients treated with statin therapy had a significantly reduced risk of ischemic stroke compared with placebo (risk ratio [RR] 0.80; 95% CI, 0.70-0.90). In addition, a linear relationship was present between measured LDL cholesterol level and the absolute risk reduction of ischemic stroke (r^2 0.90, P=.03). The study authors suggested that this supports the idea that aggressive LDL reduction further decreases risk of stroke in secondary prevention. No increased incidence of hemorrhagic stroke was noted after statin therapy. Extreme LDL lowering (mean LDL 53 mg/dL) was noted only in populations receiving both simvastatin and ezetimibe, which the study authors suggest may also indicate a nonstatin effect. EBP

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Is topical diclofenac safe in adult patients with contraindications to oral NSAID therapy?

EVIDENCE-BASED ANSWER

Probably. In patients with osteoarthritis, serious gastrointestinal or renal adverse events during topical NSAID therapy are equal to placebo (SOR: **A**, meta-analysis of RCTs and observational studies). Topical diclofenac does not result in decreased renal perfusion (SOR: **C**, disease-oriented evidence from a small cohort study). Patients with elevated risks, such as hypertension, cardiovascular disease, and DM-2, have no serious adverse events occur as well (SOR: **B**, single cohort).

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A 2018 systematic review and meta-analysis of 36 RCTs, six case-control, and one cross-sectional study (N=225,974) evaluated the efficacy and safety of topical NSAIDs in the treatment of osteoarthritis.[1] Patients included all had diagnosed osteoarthritis effecting at least one joint and were treated for at least one week. Any patients treated with combination oral and topical NSAIDs or those with ophthalmological conditions were excluded. Almost all included studies featured topical diclofenac in the form of a gel, patch, or a solution with overall treatment time and follow-up ranging from 1 to 12 weeks. It was unclear if patients treated topically had contraindications to oral therapy. The safety outcomes measured included overall adverse events, withdrawal from treatment because of adverse events, and serious adverse events such as gastrointestinal (GI) bleeding, or acute renal failure. No significant increase was observed in adverse event occurrence in patients treated with topical NSAIDs compared with the placebo group for both trials (36 trials, N=7,900; odds ratio [OR], 1.4; 95% CI, 0.99–1.9) and observational studies (7 studies, N=218,074; OR, 1.2; 95% CI, 0.9–1.6). However, after pooling of the same 31 trials, withdrawal rate from treatment because of adverse events (most common being skin reactions) was significantly higher in the topical treated group compared with placebo or no treatment (OR, 1.6; 95% CI, 1.2-2.0). Serious adverse events such as GI bleeding, acute renal failure, and symptomatic peptic ulcers were similar between the groups.

A 2019 single-center cohort study (n=24) examined the effect of oral and topical diclofenac on renal perfusion compared with baseline renal perfusion.[2] Patients were healthy volunteers without any history of renal disease or concurrent use of NSAIDS. The intervention group (n=12) received a single oral dose of 50-mg diclofenac followed by a washout period of three days and then topical application of diclofenac (Voltaren Emulgel Gel, 1.16%) over three days, whereas the control group (n=12) only received the single oral dose of 50-mg diclofenac. The outcomes measured were renal perfusion using MRI, along with plasma diclofenac levels. Topical diclofenac application did not result in relevant systemic diclofenac levels (range, 5–75 nM). Renal perfusion after topical diclofenac administration was not significantly different from baseline conditions (344 vs 388 mL/min/100 g; $P=.7$). After topical diclofenac, no adverse events were reported, and no significant changes in ALT, AST, creatinine, estimated glomerular filtration rate, or blood pressure were observed.

A 2012 multicenter, open-label, long-term safety cohort study (n=947) focused on long-term tolerability of diclofenac gel for the treatment of knee osteoarthritis in patients with hypertension, diabetes mellitus type 2 (DM-2), and cerebrovascular or cardiovascular disease.[3] About half the patients had hypertension (46%), and

more than 10% of the patients had type 2 diabetes and cerebrovascular or cardiovascular disease. Patients applied diclofenac gel 4 g to one or both knees during a one year period. After one year, the rates of gastrointestinal adverse events were similar between those with and those without hypertension (8.9% vs 7.9%). Rates were also similar for patients with type two diabetes (7%) compared with those without diabetes (8.5%) for GI adverse events. However, there was a moderate difference in the proportion of patients with cardiovascular disease (12%) who experienced GI adverse events compared with those without cardiovascular disease (7.9%). No *P* values or strength statistics were reported. EBP

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In patients with cancer-related pain, does use of cannabis reduce opioid requirements for pain control?

EVIDENCE-BASED ANSWER

Cannabis use does not appear to reduce opioid requirements for cancer-related pain (SOR: **B**, meta-analysis of low-quality randomized controlled trials and a retrospective cohort study). The European Society for Medical Oncology states that there is no clear benefit to adding medical cannabidiol to opioid therapy for cancer patients with pain (SOR: **C**, expert opinion).

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A 2019 systematic review and meta-analysis of four double-blinded, randomized, controlled trials (RCTs; N=1,361) evaluated the efficacy of cannabis-based medicines for cancer pain.[1] Individual trials included adults (mean, 58–61 years) with moderate-to-severe cancer pain and inadequate response to opioids; the trials excluded those with severe cardiovascular disease, schizophrenia, or substance use disorders. Trial size ranged from 177 to 399 patients, and duration was between two and five weeks. All RCTs were multicenter and conducted in various countries. Average daily dose of maintenance opioid therapy for all patients was between 120 and 180 morphine milligram equivalents. All intervention groups received nabiximols, a combination of tetrahydrocannabinol and cannabidiol (THC/CBD) oromucosal spray (not available in the United States) dosed as 2.7 mg THC with 2.5 mg CBD per spray, and patients took 1 to 16 sprays per day (maximum TCH/CBD dose of 43.2 mg/40 mg per day). Control group patients received a placebo spray. THC/CBD spray did not affect opioid maintenance dose (3 trials; N=970; standardized mean difference [SMD], 0.08; 95% CI, –0.1 to 0.27) or breakthrough opioid dose (3 trials; N=970; SMD, 0.08; 95% CI, –0.1 to 0.27). Overall, the reviewers considered the evidence quality to be very low as a result of uncertain or high risk of bias from inadequate allocation concealment, insufficient blinding of outcome assessment, incomplete outcome data, and small sample size. Furthermore, all studies were sponsored by the manufacturer of the THC/CBD spray.

A 2019 retrospective cohort study (n=83) examined medical records to determine the effect of cannabis on opioid requirements in adults with cancer pain treated in a palliative care clinic.[2] The study included patients who

had a urine drug screen (UDS) within 28 days of the initial visit, an opioid prescription listed in the electronic medical record, and at least one follow-up appointment within 84 days of the initial visit. It excluded patients who had a UDS positive for an illicit substance other than cannabis and those with an active prescription for codeine, tramadol, tapentadol, buprenorphine, or pentazocine. Of the 83 patients, 22 (mean age, 48 years) had UDSs that were positive for cannabis and 61 (mean age, 55 years) did not have cannabis detected by UDS. The primary end point was change in morphine equivalent daily dose (MEDD) at the 84-day follow-up visit. At 84 days, both groups demonstrated an increase in MEDD from the initial visit, but no difference in MEDD change was observed between those with and without cannabis-positive UDSs (10.8 vs 28.8 mg, respectively; $P=.69$). In addition to the small sample size and retrospective design, the study was limited by the inability to quantify the dosage, route, and frequency of cannabis use in the exposed group, and it did not correlate changes in MEDD with disease progression or other life events.

A 2018 evidence-based clinical practice guideline from the European Society for Medical Oncology noted that for patients with advanced cancer and pain that was not fully alleviated by opioid treatment, there was no clear benefit of adding nabiximols (II D recommendation: moderate evidence against efficacy based on small RCTs).[3] EBP

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Do patients with latent tuberculosis who receive direct observation treatment have higher treatment completion rates than patients who receive self-administered treatment?

EVIDENCE-BASED ANSWER

Maybe not. Direct observation treatment and self-administered treatment regimens for latent tuberculosis have similar treatment completion rates as self-administered therapy in some settings (SOR: **B**, randomized controlled trial and retrospective cohort).

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A 2017 multicenter, noninferiority randomized controlled trial (n=1,002) compared the effectiveness of self-administered treatment with direct observation treatment of latent tuberculosis (TB) infection.[1] Patients were adult men and nonpregnant women diagnosed with latent TB from the United States, Spain, China, or South Africa. Patients with active TB, any prior TB treatments lasting longer than one week, and those with an HIV infection currently on antiretrovirals were excluded. Patients were randomized to receive once-weekly treatment by direct observation treatment (n=337), self-administered treatment weekly with text message reminders (n=328), and self-administered treatment weekly without text reminders (n=337). All groups were treated with a fixed dose of 900 mg each of isoniazid and rifapentine once weekly. The primary outcome measured was treatment completion rate, defined as taking 11 doses within 16 weeks. The protocol team selected

a decrease in treatment completion of 15% or less as the noninferiority margin. Treatment completion rate was higher in the direct observation group compared with both the self-administration group with reminders (mean difference [MD] 11%; 95% CI, 3.1% to 19%) and the self-administration group without reminders (MD 13%; 95% CI, 4.5% to 22%). However, these manually calculated MDs between groups did not exceed the defined 15% margin for noninferiority. Limitations include not being generalizable to high TB burden countries, not including pediatric patients, and not representing underserved populations, given that 64% completed high school, 5.1% were homeless, 61% were employed, and 91% had a cell phone with texting capability.

A 2019 single-center, retrospective cohort with a nested case-control study (N=144) evaluated completion rates and tolerability of once-weekly 900 mg isoniazid and rifapentine to treat latent TB in adults.[2] Patients were included if they attended at least one follow-up visit and were not currently on another TB treatment regimen. Treatment lasted a total of 12 weeks, with 111 patients receiving direct observation and 33 self-administering the treatment. Completion of therapy was defined as a patient taking 11 of 12 doses within the 16 weeks of treatment. Patients in the self-administered treatment group did not receive weekly reminders for medication administration; however, some providers encouraged patients to send messages after each dose. A total of 119 patients (83%) completed the treatment regimen. No significant difference was observed between the direct observation group and the self-administer group for completion of treatment (83% vs 82%, $P=.89$). Patients experienced several adverse drug reactions (64%, n=92), including flu-like symptoms (38%) and gastrointestinal symptoms (32%). Self-administered treatment patients experienced adverse drug reactions one week before direct observation treatment patients on average. Limitations included the retrospective study design and the smaller cohort of self-administered treatment patients in comparison with the direct observation treatment patients. EBP

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What are the benefits and risks of hormone replacement therapy for primary prevention of chronic conditions in postmenopausal women?

EVIDENCE-BASED ANSWER

Combined hormone replacement therapy (HRT) for at least one year in perimenopausal or postmenopausal women is associated with an increased risk of myocardial infarction (MI), venous thromboembolism (VTE), stroke, and breast cancer. Estrogen-only HRT has a small benefit of decreasing MI and breast cancer risk but increases VTE and stroke risk (SOR: **A**, based on a meta-analysis of randomized controlled trials [RCTs]). An increased risk of gallbladder disease, dementia, and urinary incontinence and a decreased incidence of diabetes and fractures with either combined HRT or estrogen alone was noted (SOR: **A**, based on a meta-analysis of RCTs). Younger initiation of HRT (<60 years old) is associated with a decrease in all-cause mortality and cardiac mortality but an increase in cerebrovascular events (SOR: **A**, based on a meta-analysis of RCTs).

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A 2019 meta-analysis of 31 randomized controlled trials (RCTs; N=40,521) evaluated the benefits and harms of hormone replacement therapy (HRT, estrogen alone or combined estrogen and progesterone) when HRT was initiated in younger (<60 years old) and older women (>60 years old).[1] The analysis included 23 double-blinded placebo-controlled, six open-labelled, one partly double-blinded and partly open-label, and one observer blinded studies. The trials included perimenopausal and postmenopausal women (mean 59.7 years old) randomized to receive daily systemic estrogen or combined estrogen and progesterone for variable follow-up times between studies (mean 3.2 years). HRT formulations, dosing, and route of administration varied between studies. The primary endpoints included all-cause mortality, cardiac mortality, coronary heart events (a composite of cardiac mortality and nonfatal myocardial infarction [MI]), and a composite of stroke, transient ischemic attack, and systemic embolism. All-cause mortality (16 trials, N=12,790, odds ratio [OR] 0.72; 95% CI, 0.57–0.91; number needed to treat [NNT]=100) and cardiac mortality (8 trials, N=10,775, OR 0.61; 95% CI, 0.37–1.0; NNT=333) were reduced when HRT was initiated in younger women. Exclusion of the open-label trials erased the cardiac benefit. Both groups experienced an increase in cerebrovascular events (18 trials, N=36,844, OR 1.5; 95% CI, 1.4–1.7; NNH=56). Limitations included the lack of a defined way of endpoint data collection, lack of proximity to timing of menopause, wide variability in medication formulation, route of administration, and variability in follow-up times.

A 2017 meta-analysis of 22 double-blinded RCTs (N=43,637) evaluated the benefits and harms of HRT.[2] The trials included perimenopausal or postmenopausal women (range 26–91 years old, mean ages 48–76 years old) randomized to receive varying HRT doses and formulations (estrogens, with or without progestogens, via the oral, transdermal, subcutaneous, vaginal, or intranasal route) or placebo taken for at least one year. Most of the participants were postmenopausal American women over 60 years old with comorbidities. Follow-up varied between one and 5.6 years for combined HRT and 1 to 7.1 years for the estrogen-only arm. Combined HRT increased the risk of breast cancer, MI, stroke, and VTE. Estrogen alone decreased MI and invasive breast cancer but increased the risk of stroke and VTE (see **TABLES 1 and 2**). The main limitation was only 30% of women were 50 to 59 years old (a prime age for HRT for vasomotor symptoms).

A 2017 meta-analysis of 18 RCTs (N=40,058) examined the benefits and harms of HRT.[3] The analysis included published and unpublished original research, RCTs, controlled clinical trials, systematic reviews, and large controlled cohort studies (>10,000 women). Although some studies were included in the 2017 meta-analysis above, additional outcomes were evaluated. Generally healthy perimenopausal and postmenopausal women (mean ages 53–79 years old, majority Caucasian) received one year or more of estrogen-only formulations or combination preparations of estrogen plus progestin for the primary prevention of chronic conditions, placebo, or no treatment. The average follow-up in trials was 3.5 years. Stroke, VTE, gallbladder disease, and urinary incontinence increased with estrogen alone

TABLE 1. Harms and benefits of combined hormone replacement therapy in perimenopausal or postmenopausal patients[2,3]

Combined estrogen and progesterone therapy	Meta-analysis of 22 RCTs			Meta-analysis of 18 RCTs		
Harms	**No. of trials/patients**	**RR (95% CI)**	**NNH**	**No. of trials/patients**	**RR (95% CI)**	**NNH**
Breast cancer (invasive)	1/16,608	1.3[a] (1.0–1.6)	200	1/16,608	1.3[a] (1.0–1.6)	188
Lung cancer/death from lung cancer	1/16,608	1.7 (1.2–2.6)	250	1/16,608	1.1 (0.77–1.5)	2,000
Coronary heart disease	2/20,993	1.9[a] (1.2–3.1)	500	3/18,218	1.2 (1.0–1.5)	243
Dementia (probable)		—	—	1/4,532	1.97[a] (1.2–3.3)	113
Gallbladder disease	1/14,203	1.6[a] (1.3–2.1)	91	1/14,203	1.6[a] (1.3–1.97)	86
Stroke	2/17,585	1.5[a] (1.0–2.1)	500	1/16,608	1.4[a] (1.1–1.8)	188
VTE	2/20,993	4.3[a] (2.5–7.3)	200	1/16,608	1.95[a] (1.5–2.5)	83
Urinary incontinence		—	—	1/5,182	1.4[a] (1.3–1.5)	11
All-cause mortality		—	—	3/19,580	1.0 (0.88–1.2)	2,500
Benefits	**No. of trials/patients**	**RR (95% CI)**	**NNT**	**No. of trials/patients**	**RR (95% CI)**	**NNT**
Colorectal cancer		—	—	1/16,608	0.64[a] (0.44–0.91)	303
Fractures (osteoporotic)	1/16,608	0.78[a] (0.71–0.86)	42	5/20,499	0.80[a] (0.68–0.94)	45
Diabetes		—	—	1/15,874	0.84[a] (0.72-0.97)	129

[a] Statistically significant. RR=relative risk; NNT=number needed to treat; NNH=number needed to harm; RCT=randomized controlled trial; VTE=venous thromboembolism.

TABLE 2. Harms and benefits of estrogen-alone hormone replacement therapy in perimenopausal or postmenopausal patients[2,3]

Estrogen therapy	Meta-analysis of 22 RCTs			Meta-analysis of 18 RCTs		
Harms	No. of trials/patients	RR (95% CI)	NNH	No. of trials/patients	RR (95% CI)	NNH
Colorectal cancer		—	—	1/10,739	1.2 (0.81–1.6)	625
Lung cancer		—	—	1/10,739	1.0 (0.73–1.5)	2,000
Dementia (probable)		—	—	1/2,947	1.5 (0.84–2.7)	158
Gallbladder disease	1/8,376	1.8[a] (1.4–2.2)	50	1/8,376	1.6[a] (1.3–2.0)	47
Stroke	1/10,739	1.3[a] (1.1–1.7)	125	1/10,739	1.3[a] (1.1–1.7)	126
VTE	1/10,739	2.2[a] (1.1–4.4)	333	1/10,739	1.4[a] (1.1–1.9)	128
Urinary incontinence		—	—	1/3,073	1.5[a] (1.4–1.7)	8
All-cause mortality		—	—	3/11,961	1.0 (0.88–1.2)	1,666
Benefits	**No. of trials/patients**	**RR (95% CI)**	**NNT**	**No. of trials/patients**	**RR (95% CI)**	**NNT**
Breast cancer (invasive)	1/8,376	0.79 (0.61–1.0)	200	1/10,739	0.79[a] (0.61–1.0)	188
Coronary heart disease	1/10,739	0.94 (0.78–1.1)	333	3/11,310	0.95 (0.79–1.1)	500
Fractures (osteoporotic)	1/10,739	0.73[a] (0.65–0.80)	26	1/10,739	0.73[a] (0.65–0.80)	26
Diabetes		—	—	1/9,917	0.87[a] (0.77–0.98)	73

[a] Statistically significant. RR=relative risk; NNT=number needed to treat; NNH=number needed to harm; RCT=randomized controlled trial; VTE=venous thromboembolism.

and combined HRT. Combined HRT additionally increased the risk of MI, invasive breast cancer, and probable dementia (**TABLES 1 and 2**). Limitations included high attrition rates, low adherence to medications, and the inclusion of various study designs when calculating outcomes. EBP

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