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EVIDENCE-BASED PRACTICE

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FPIN
Family Physicians Inquiries Network

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SPOTLIGHT ON PHARMACY

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

STATEMENT OF PURPOSE

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

EDITORIAL POLICY

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DISCLOSURE

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What type of infant formula is best to prevent atopic diseases?

CASE STUDY

A G3P3 woman comes to clinic with her six-month-old baby for a well-child visit. The baby is exclusively formula-fed without any issues. Her older children have severe allergies and the mother asks if hydrolyzed formula would help decrease the risk of development of allergies in her baby.

DOI 10.1097/EBP.0000000000001349

Evidence-Based Answer

Currently, no consistent evidence exists that the use of either partially or exclusively hydrolyzed formula with or without prebiotics can prevent atopic disease in infants and children at high risk for allergic disease. The American Academy of Pediatrics has updated its clinical report in 2019 by stating that hydrolyzed formula is no longer considered protective of atopic dermatitis in infants.[1]

Evidence Summary

A 2016 systematic review and meta-analysis of 37 prospective trials with 19,000 patients compared allergic outcomes in infants receiving partially or extensively hydrolyzed cows' milk formula or standard formula and human milk.[2] The pooled data showed no decreased risk of 0 to 4 years old (odds ratio [OR] 0.84; 95% CI, 0.67–1.1) and age 5 to 14 (OR 0.86; 95% CI, 0.72–1.0); no decreased risk of wheezing at age 0 to 4 (OR 0.82; 95% CI, 0.48–1.4) or at age 5 to 14 (OR 0.99; 95% CI, 0.65–1.5); no decreased risk of allergic rhinitis at age 5 to 14 (OR 1.0; 95% CI, 0.82–1.3); and no decreased risk of food allergy or sensitization at age 0 to 4 (OR 1.09; 95% CI, 0.57–2.08). There seemed to be a decreased risk of allergic rhinitis with hydrolyzed cow's milk at age 0 to 4 (OR 0.61; 95% CI, 0.44–0.84). Limitations included several studies that included multifaceted intervention beyond hydrolyzed formula and many with high risk of bias.

A 2011 single-blind (participant), randomized controlled trial compared allergic outcomes in 620 high-risk (family history of allergic disease including eczema, asthma, allergic rhinitis or food allergy) infants fed a conventional cow's milk formula versus a partially hydrolyzed whey formula or a soy-based formula at the partial or complete cessation of breastfeeding or if formula feeding only.[3] Development of allergic manifestations were measured 18 times in the first two years of life, and skin prick tests to six common allergens were performed at 6, 12, and 24 months. The primary outcome was any allergic manifestation in the first two years of life. Secondary outcomes included development of allergic manifestations through ages 6 and 7 years old. No evidence exists that hydrolyzed whey (OR 1.2; 95% CI, 0.81–1.8) or soy formula (OR 1.3; 95% CI, 0.84–1.9) reduced the risk of allergic manifestations in the first two years of life. Similarly, no difference was noted between the groups on any secondary outcomes or two-year period prevalence at ages 6 and 7 years old. Limitations of this study included the use of some parent-reported outcomes that have not been validated.

Furthermore, a 2016 double-blind, randomized controlled trial compared a prebiotic-supplemented partially hydrolyzed whey formula to standard cow's milk formula in cumulative incidence of eczema for infants with a family history of allergic disease who received formula milk before age of four weeks (early introduction subgroup).[4] Secondary outcomes included the cumulative incidence of eczema by 12 or 18 months of age in all infants randomized. Infants were randomized to active (n=432) or control (n=431) formula until six months of age if formula was introduced before 18 weeks. A total of 1,047 infants were enrolled and 82% (863) had formula introduced before 18 weeks and 72% (758) were randomized to the "early introduction subgroup." In the early introduction subgroup, eczema occurred by 12 months in 28% (84 of 293) of infants in the active group and 29% (93 of 324) of infants in the control group (OR 0.98; 95% CI, 0.68 to 1.4). In all infants randomized, eczema occurred by 12 months in 31% (107 of 347) of the active groups versus 30% (112 of 370) in the control groups (OR 0.99; 95% CI, 0.71 to 1.4). One limitation of the study was that it combined two different interventions (partially hydrolyzed formula and prebiotic supplementation).

CASE CONCLUSION

You let the mother know that no need to change from regular formula to hydrolyzed formula, even in infants at high risk for allergies. EBP

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References

1. Greer FR, Sicherer SH, Burks AW. The effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, hydrolyzed formulas, and timing of introduction of allergenic complementary foods. *Pediatrics*. 2019;143(4):e20190281. [STEP 5]
2. Boyle RJ, Ierodiakonou D, Khan T, et al. Hydrolysed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis. *BMJ*. 2016;352:i974. [STEP 1]
3. Lowe AJ, Hosking CS, Bennett CM, et al. Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol.* 2011;128(2):- 360-365.e4. [STEP 2]
4. Boyle RJ, Tang ML, Chiang WC, et al; PATCH study investigators. Prebiotic-supplemented partially hydrolysed cow's milk formula for the prevention of eczema in high-risk infants: a randomized controlled trial. *Allergy*. 2016;71(5):701-710. [STEP 2]

In women requiring chronic anticoagulation, are the DOACs better than warfarin in decreasing the incidence of anticoagulation-associated HMB?

EVIDENCE-BASED ANSWER

No. The relative occurrence of vaginal bleed is comparable in women treated with apixaban or warfarin (SOR: **B**, secondary analysis of a randomized controlled trial and retrospective cohort study). Rivaroxaban may be associated with an increased likelihood of heavy menstrual bleeding compared with apixaban (SOR: **B**, retrospective cohort study).

DOI 10.1097/EBP.0000000000001515

A 2017 secondary analysis of a prospective randomized double-blind controlled trial (n=2,228) examined the incidence of abnormal uterine bleeding while on apixaban or warfarin in female patients with acute venous thromboembolism (VTE).[1] Patients were a mean age of 45 years old with symptomatic proximal deep-vein thrombosis (DVT), pulmonary embolism, or both. Women were treated with apixaban 10 mg twice daily for seven days, followed by 5 mg twice daily for six months (n=1,122) or warfarin with an INR goal of 2 to 3 for six months (n=1,106). Clinically relevant nonmajor vaginal bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with a medical intervention, unscheduled contact with a physician, interruption of study drug, or discomfort or impairment in carrying out activities of daily life. Major vaginal bleeding was defined as overt bleeding, either associated with a fall in hemoglobin level of at least 2 g/dL or requiring transfusion of at least two units of erythrocytes. No difference was noted in nonmajor bleeding between those receiving apixaban versus warfarin (odds ratio [OR] 1.2; 95% CI, 0.7–2.0). The occurrence of major vaginal bleeding, prolonged bleeding, intermenstrual bleeding, heavy menstrual bleeding (HMB), and anemia were comparable between both treatment groups.

A 2020 retrospective cohort study (n=195) assessed the impact of oral anticoagulation on menstrual-associated bleeding in female patients receiving rivaroxaban, apixaban, or warfarin over a period of six years.[2] These women were between 18 and 50 years old, mostly White, and with a new prescription for oral anticoagulation for VTE treatment. Patients were analyzed from a single tertiary care center and its affiliated clinics from Portland, Oregon. Sixty-two patients were prescribed rivaroxaban, 54 were prescribed apixaban, and 79 were prescribed warfarin (dosing not available). Approximately 13% of women had a documented history of HMB, defined as menstrual bleeding that required intervention of some kind. In addition, 32% of the patients needed treatment for uterine bleeding within six months of starting anticoagulation. The medical and surgical therapies for treatment of HMB included hormonal therapy, antifibrinolytic therapy, modification of anticoagulation, blood transfusion, ablation, uterine artery embolization, hysterectomy, or hysteroscopy. Most patients requiring an intervention were taking rivaroxaban (44%) as compared with apixaban (22%) and warfarin (34%). Heavy menstrual bleeding was similar in apixaban and warfarin groups (OR 1.02; 95% CI, 0.87–1.2). After controlling for demographic and baseline bleeding levels, patients treated with rivaroxaban were more likely to have a HMB event as compared with apixaban (OR 1.4; 95% CI, 1.1–1.8). Independent of the type of anticoagulation, patients with a history of HMB were more likely to have HMB when compared with patients with normal menses or no documented history (OR 1.8; 95% CI, 1.5–2.2). One limitation of this study was that variables known to increase risk of bleeding, such as platelet count or function, were not considered. EBP

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References

1. Brekelmans M, Scheres L, Bleker S. Abnormal vaginal bleeding in women with venous thromboembolism treated with apixaban or warfarin. *Thromb Haemost.* 2017;117(4): 809-815. [STEP 3]
2. Samuelson Bannow B, Chi V, Sochacki P. Heavy menstrual bleeding in women on oral anticoagulation. *Thromb Res.* 2021;197:114-119. [STEP 3]

Ibuprofen, a slight edge over Tylenol, in fever and pain reduction in children younger than two years old

Tan E, Braithwaite I, McKinlay CJD, Dalziel SR. Comparison of acetaminophen (paracetamol) with ibuprofen for treatment of fever or pain in children younger than 2 years: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3(10):e2022398.

DOI 10.1097/EBP.0000000000001465

This study is a meta-analysis of 19 studies published between 1994 and 2018, which included a total of 241,138 children from multiple countries in hospital and community-based settings. Twelve of the studies were randomized and compared ibuprofen to acetaminophen with outcomes of fever and pain reduction in children <2 years old. The primary outcome assessed was temperature reduction by four hours (4 studies with 435 participants; standardized mean difference [SMD] 0.38; 95% CI, 0.08–0.67; $P=.01$; $I^2=49\%$; moderate quality evidence). Secondary outcomes were continuous variables for fever from 4 to 24 hours (5 studies with 879 patients; SMD 0.24; 95% CI, 0.03–0.45; $P=.03$; $I^2=57\%$; moderate-quality evidence) and pain from 4 to 24 hours (2 studies with 535 patients; SMD 0.20; 95% CI, 0.03–0.37; $P=.02$; $I^2=25\%$; moderate-quality evidence). Serious adverse outcomes (including kidney impairment, gastrointestinal bleeding, hepatotoxicity, severe soft tissue infection, empyema, and asthma/or wheezing) were uncommon and similar between ibuprofen and acetaminophen groups (7 studies with 27,932 patients; odds ratio 1.08, 95% CI, 0.87–1.33; $P=.50$; $I^2=0\%$; moderate-quality evidence). The studies were evaluated by two independent authors and included if >50% of patients in the study were <2 years old, and the study reported the primary or secondary outcomes. Disagreements between investigators were resolved by conversation or by a third investigator. Statistical heterogeneity was calculated using a fixed-effect method if the I^2 was <50% and using a random-effect method if I^2 was 50% or greater.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. (https://journals.lww.com/ebp/Documents/PURLs%20Methods%20AC.pdf)

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

Bottom line: These results favor ibuprofen over acetaminophen in both primary and secondary outcomes with similar low rates of serious adverse effects. However, the studies were limited by heterogeneity, and clinical importance of temperature or pain differences between the medications remains unclear.

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The authors declare no conflicts of interest.
The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the U.S. Army Medical Department, the Army at large, or the Department of Defense.

Testosterone to prevent or treat type 2 diabetes? Not yet

Wittert G, Bracken K, Robledo KP, et al. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. *Lancet Diabetes Endocrinol*. 2021;9(1):32-45.

DOI 10.1097/EBP.0000000000001542

This paper was a randomized, double-blind, placebo-controlled, two-year phase IIIB trial investigating testosterone treatment to prevent progression to or reverse early type 2 diabetes (T2DM) conducted in six Australian tertiary care centers. This paper included men 50 to 74 years old who had a waist circumference of >95 cm (37 inches), a serum testosterone concentration <14.0 mmol/L (403.8 ng/dL) without pathological hypogonadism, and newly

diagnosed impaired glucose tolerance (2-hour oral glucose tolerance test [OGTT] 7.8–11.0 mmol/L [140.4–199.8 mg/dL]) or T2DM (2-hour OGTT between 11.1 and 15 mmol/L [198.0–270 mg/dL]). The primary outcomes of interest were two-hour OGTT >11.1 mmol/L (198.0 mg/dL) and mean change from baseline two-hour OGTT at two years. Prespecified serious adverse events of interest included cardiovascular, prostate, depression, and cancer-related events and death from any cause. Exclusion criteria included high risk for cardiovascular disease, previous testosterone treatment, use of medication affecting the hypothalamic-pituitary axis, current or history of cancer, abnormal liver function, decreased renal function, history of bariatric surgery, recent treatment with antiobesity medication, and previous diagnosis of type 1 or type 2 diabetes. All patients were enrolled in a lifestyle program through Weight Watchers (formerly, Weight Watchers) and were randomly assigned to receive intramuscular testosterone undecanoate (1,000 mg) or placebo at baseline, six weeks, and every three months for two years. At the two-year evaluation, 12% of the intervention group and 21% of the placebo group continued to have two-hour OGTT >11.1 mmol/L (risk ratio 0.59; 95% CI, 0.43–0.80; $P=.007$). The mean change from baseline two-hour OGTT was –0.95 mmol/L in the placebo group and –1.70 mmol/L in the testosterone group (mean difference –0.75 mmol/L, CI, –1.1 to –0.40; $P<.0001$). The number needed to treat for the endpoint hematocrit ≥54% was 4.8, and prostate-specific antigen of ≥0.75 μg/mL was 33 in the testosterone group. However, no statistically significant between-group differences were observed in cardiovascular events or prostate cancer over the study period.

Methods

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

Bottom line

This study focused on a low-risk patient population who received a non-Food and Drug Administration–approved dose of testosterone undecanoate for the treatment of early T2DM. The results focused on a disease-oriented outcome, improving two-hour OGTT, and was not designed to investigate delaying or preventing the long-term microvascular and macrovascular disease outcomes of greatest concern for patients with diabetes. Without data specifically investigating testosterone compared with gold standard treatments for early T2DM, that is, metformin, it is too early to recommend this intervention.

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

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Oh! My aching statin

Herrett E, Williamson E, Brack K, et al. Statin treatment and muscle symptoms: series of randomized, placebo-controlled n-of-1 trials. *BMJ*. 2021;372:n135.

DOI 10.1097/EBP.0000000000001523

This series of n-of-1 trials conducted in the United Kingdom assessed the effect of statin medications compared with placebo on self-reported muscle symptoms in patients who had previously stopped or considered stopping a statin because of muscle symptoms (N=200). The study excluded patients with generalized persistent unexplained muscle pain, a history of transaminitis above three times the upper limit of normal, or a previous creatinine kinase above five times the upper limit of normal. Those included were mostly men (58%) with a history of cardiovascular disease (70%).

Patients were assigned to a random order of six 2-month trial periods of atorvastatin 20 mg daily or placebo. The primary outcome was daily self-reported muscle pain, stiffness, cramping, or weakness on a modified 10-point visual analog scale, reported for the last seven days of each trial period. A secondary outcome was whether patients resumed statin treatment after reviewing individualized results, revealed three months after the end of the final trial period.

Forty-nine patients did not provide enough data to be included in the primary analysis. No difference existed in the mean muscle symptom scores between the statin and placebo periods (mean difference –0.11; 95% CI, –0.36 to 0.15; $P=.40$). Of the 113 patients who reviewed their results with primary care physician, 99 of 113 (88%) said the trial was helpful and 74 of 113 (66%) said they would resume statin treatment. Eighty withdrawals were noted during the study, with no significant difference between groups. Withdrawals for intolerable muscle symptoms were uncommon and not different between groups (9% in the statin group vs 7% in the placebo group; relative risk 1.38; 95% CI, 0.66–2.8; $P=.56$). Atorvastatin 20 mg was the only statin used in this study.

Methods

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

An additional literature search was conducted by searching (UpToDate and PubMed with the terms myalgias in statins, n-of-1 study) 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	No
Change in practice	No	Clinically meaningful	No

Bottom line

No difference exists in muscle symptoms reported during the use of atorvastatin 20 mg daily compared with placebo in patients who previously reported muscle pain while taking a statin. An n-of-1 trial structure may inform patients and physicians about an individual's medication tolerance, but this approach is not immediately implementable in most practices. Many clinicians already recommend a re-trial of statins after discontinuation, and the results of this study only apply to a single moderate dose statin.

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Giving methamphetamine treatment a shot in the arm: Bupropion and naltrexone in methamphetamine use disorder

Trivedi MH, Walker R, Ling W, et al. Bupropion and Naltrexone in Methamphetamine Use Disorder. *N Engl J Med*. 2021;384(2):140-153. doi: 10.1056/NEJMoa2020214

DOI 10.1097/EBP.0000000000001580

This multicenter, double-blind, two-stage, placebo-controlled trial (n=403) evaluated weekly extended-release naltrexone (380 mg every three weeks) and daily extended-release bupropion (450 mg/d) together in reducing urine tested methamphetamine use over 12 weeks (six weeks for each stage) in adults 18 to 65 years old who wanted to quit or reduce methamphetamine use.

Researchers enrolled patients with moderate-to-severe amphetamine use disorder with confirmatory urine testing. Negative urine testing for opioids was required at enrollment. Patients were excluded if already enrolled in substance use disorder therapy or had an expected opioid need in the next 90 days. The power analysis for 90% confidence indicated a need for 400 participants.

In stage 1,403 patients were randomly assigned in a 0.26:0.74 ratio to receive naltrexone–bupropion or matching injectable and oral placebo for six weeks. Those in the placebo group who did not respond in stage 1 underwent re-randomization in stage 2 (n=225) and were assigned in a 1:1 ratio to receive naltrexone–bupropion or placebo for another six weeks. All groups were analyzed by intention-to-treat analysis. Overall, demographics showed 68.7% male, 71% white, 70.6% daily nicotine use, mean PHQ-9=19.9 and mean age of 41 years old.

Researchers chose a primary outcome of three or four out of four amphetamine urine tests negative when checked at weeks 5, 6, 11, and 12. Weighted response rates across stages 1 and 2 are 13.6% in the treatment group and 2.5% in the placebo group. Total treatment effect is 11.1% ($P<.001$; number needed to treat [NNT]=9). Adverse events occurred more frequently with naltrexone–bupropion: nausea (32.9% vs 11.3%, $P<.001$), vomiting (11.2% vs 2.4%, $P<.001$), dizziness (10.1% vs 2.7%, $P=.006$), and constipation (9.2% vs 2.4%, $P=.005$). However, adherence was high and attrition rate was low in both groups (numbers not provided).

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described at https://journals.lww.com/ebp/Documents/PURLs%20Methods%20AC.pdf.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting (in a selected population)	Yes
Valid	Yes	Implementable	Yes
Change in practice	Yes	Clinically meaningful	Yes

Bottom line: In patients with methamphetamine use disorder, weekly extended-release naltrexone and daily bupropion can reduce repeated methamphetamine use (NNT=9) over a 12-week period in conjunction with standard counseling.

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Let us get therapeutic: Anticoagulation dosing in high-risk hospitalized patients with COVID-19

Efficacy and safety of therapeutic-dose heparin versus standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19

Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin versus standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: The HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021:e216203. DOI 10.1097/EBP.0000000000001614

KEY TAKEAWAY: Empiric therapeutic-dose anticoagulation significantly reduces the risk of venous and arterial thromboembolism (ATE) and death in hospitalized, noncritically ill patients with COVID-19 with D-dimer four times the upper limit of normal.

STUDY DESIGN: Multicenter, active control double-blinded randomized clinical trial.

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Hospitalized patients with COVID-19 are at increased risk of thromboembolism. Empiric therapeutic anticoagulation has not been shown to be of significant benefit for those patients who are admitted to the intensive care unit (ICU). However, only limited research is present on whether the same is true for noncritically ill patients.

PATIENTS: Adults hospitalized with COVID-19
INTERVENTION: Empiric therapeutic enoxaparin
CONTROL: Standard prophylactic enoxaparin or unfractionated heparin
OUTCOME:
Primary outcome: incidence of venous thromboembolism (VTE), ATE, or death from any cause within 30 days of study randomization
Secondary outcomes: major bleeding, rehospitalization, intubation, extracorporeal membrane oxygenation (ECMO) use, nonfatal cardiac arrest, progression to acute respiratory distress syndrome (ARDS), or primary efficacy outcome at day 14 of hospitalization.

METHODS BRIEF DESCRIPTION:
- Study patients were nonpregnant adults 18 years or older hospitalized with COVID-19 from May 8, 2020, through May 14, 2021.
  - Patients were on supplemental oxygen and had a D-dimer level greater than four times the upper limit of normal (based on local laboratory criteria) or a sepsis-induced coagulopathy score of 4 or greater.
  - Patients were excluded if they were determined to need full-dose anticoagulation or dual antiplatelet therapy on admission, had bleeding within the past month or had a current bleed, platelet count less than 25,000/Ul, or a history of heparin-induced thrombocytopenia within 100 days.
- Empiric therapeutic enoxaparin treatment was started after study randomization and stopped at the time of hospital discharge or if the primary outcome or any secondary outcome occurred.
  - Intervention: empiric therapeutic enoxaparin dosed (1 mg/kg) subcutaneously twice daily if creatinine clearance was greater than 30 mL/min or 0.5 mg/kg if creatinine clearance was 15 to 29 mL/min.
  - Comparison: standard prophylactic enoxaparin (30–40 mg subcutaneously daily) or unfractionated heparin dosing per institutional policy.
- All patients underwent lower extremity Doppler ultrasound at hospital day 10 to 14 or at discharge if it was sooner. This also occurred at 28 to 32 days after randomization.

INTERVENTION (# IN THE GROUP): 129
COMPARISON (# IN THE GROUP): 124
FOLLOW-UP PERIOD: 28 to 32 days

RESULTS:
Primary Outcomes:
- For non-ICU patients, therapeutic enoxaparin decreased the risk of VTE, ATE, and death compared with prophylactic enoxaparin (17% vs 36%, respectively; risk ratio [RR] 0.46; 95% CI, 0.27–0.81; number needed to treat=5; number needed to harm=2,000).
- For ICU patients, therapeutic enoxaparin did affect the risk of VTE, ATE, or death compared with prophylactic

enoxaparin (51% vs 55%, respectively; RR 0.92; 95% CI, 0.62–1.4).

Secondary Outcomes:

- No significant difference was observed between the two groups for secondary outcomes, including major bleeding, rehospitalization, or nonfatal cardiac arrest.

LIMITATIONS: This study may not be generalized to less acutely ill patients with COVID-19. EBP

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The author declares no conflicts of interest.
The opinions and assertions contained herein are those of the author and are not to be construed as official or as reflecting the views of the U.S. Navy Medical Department, the Navy at large, or the Department of Defense.

Should I give my hospitalized patients remdesivir?

Remdesivir for the treatment of COVID-19 (review)

Ansems K, Grundeis F, Dahms K, et al. Remdesivir for the treatment of COVID-19. *Cochrane Database Syst Rev*. 2021; 8(8):CD014962. doi:10.1002/14651858.CD014962 DOI 10.1097/EBP.0000000000001622

KEY TAKEAWAY: Remdesivir has no effect on mortality or clinical course for hospitalized patients.

STUDY DESIGN: Meta-analysis of five RCTs (N=7,142).

LEVEL OF EVIDENCE: STEP 1.

BACKGROUND: Remdesivir is a broad-spectrum antiviral medication that was given emergency use authorization in approximately 50 countries for the treatment of COVID-19 pneumonia. It later became the first drug approved by the U.S. Food and Drug Administration for the treatment of COVID-19. The average cost of a 10-day regimen is estimated at $6,864. The World Health Organization began to recommend against its use in November 2020 after evaluating it in their Solidarity Trail. The drug seems to have no effect on hospital stay or mortality and has a well-known adverse effect of elevating liver enzymes.

PATIENTS: Hospitalized adults with confirmed SARS-CoV-2 infection.
INTERVENTION: Ten-day course of remdesivir.
CONTROL: Placebo or usual care.
OUTCOME: All-cause mortality.

METHODS BRIEF DESCRIPTION:

- The review included five RCTs, four of which reported on the primary outcome of all-cause mortality up to day 28.
- The patient population included hospitalized adults confirmed to be infected with COVID-19 irrespective of treatment setting, gender, ethnicity, or disease severity.
- The remdesivir group received a loading dose of 200 mg, then 100 mg daily thereafter for a total of 10 days.
- The primary outcome of all-cause mortality was observed up to 28 days.
- Several secondary outcomes were assessed by the researchers (including improvement in clinical status and clinical worsening), but an insufficient number of trials reported on these data for meta-analysis. For this reason, only the primary outcome is summarized here.

INTERVENTION (# IN THE GROUP): 3,635.
COMPARISON (# IN THE GROUP): 3,507.
FOLLOW-UP PERIOD: At or up to day 28.

RESULTS: Remdesivir had no impact on all-cause mortality compared with placebo up to day 28 (4 trials, N=7,142; RR 0.93; 95% CI, 0.81–1.1).

LIMITATIONS: A risk for bias is present because of missing data—these studies were carried out during a pandemic and often on patients in clinical extremis. The effect of remdesivir on COVID-19 patients early in their illness was not addressed. EBP

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Are corticosteroid injections better than conservative treatment in patients with trigger finger?

EVIDENCE-BASED ANSWER

In managing trigger finger, corticosteroid injections are better than placebo, hyaluronic acid injections, physical therapy, and shockwave therapy in the short term (1–3 months) and similar to nonsteroidal anti-inflammatory injections in the long term (>4 months; SOR: **B**, meta-analysis of low-quality randomized controlled trials). Metacarpal blocking orthotics perform moderately well and decrease need for steroid injections (SOR: **C**, limited evidence from a case series in a systematic review).

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A 2020 meta-analysis of 16 randomized controlled trials (RCTs; N=1,185) evaluated multiple treatment strategies for the treatment of trigger finger.[1] A subanalysis highlighted 12 trials (N=567) specifically examining cortisone injections as treatment. Patients were nondiabetic adults, predominantly female with a mean age of 57 years old and had unspecified severity of trigger finger. Three trials (N=59) compared a variety of steroid injections and doses (methylprednisolone acetate 20 mg; betamethasone 6 mg; triamcinolone 1 mL or 0.9% NaCl) with placebo, measuring complete resolution of pain and triggering over a period of 1 week to 12 months. Patients treated with steroids had greater rates of resolution at four weeks (relative risk [RR] 3.7; 95% CI, 1.6–8.5), but efficacy became nonsignificant at four months (RR 3.2; 95% CI, 0.9–11.8) compared with placebo. Two trials (N=110) investigated steroid injections compared with physiotherapy treatments for 10 sessions, including ultrasound, stretching muscle exercises, and massage. Patients in the corticosteroid group were significantly more likely to report pain relief at three months compared with those in the physiotherapy group (odds ratio [OR] 17.4; 95% CI, 2.1–144). Two trials measuring corticosteroid injections compared with NSAID injections had no difference in the long-term effects (>4 months). Steroid injections (n=50) were also compared with hyaluronic acid injections (n=52), which initially showed more benefit in the steroid group, but results were similar at six months.

A 2017 systematic review (n=297) of one RCT, five cohort studies, and one pilot study investigated the efficacy of orthotic management of trigger finger.[2] Patients were predominantly female with a mean age of 63 years old, and follow-ups varied from 6 weeks to 1 year. The fingers commonly affected were middle and ring followed by the thumb. Six studies (N=276) examined metacarpal phalangeal joint immobilization using custom-made thermoplastic orthoses. Depending on pain and triggering episodes, the orthotic was worn day and night for six weeks (range of 3–12 weeks). No data or specifics were reported on control groups. Primary outcomes were measured via different standardized scales and reported as effect sizes. Moderate to large, significant effect sizes, ranging from 0.49 to 1.99, were reported in all studies on pain reduction in orthotic groups. All authors described reduction in patient-reported triggering symptoms ranging from 47% to 93%. One study (n=46) reported reoccurrence of symptoms, with 13% receiving steroid injection or surgical intervention. In the year after orthotic removal, four patients had trigger finger steroid injections and two patients had an A1 pulley surgical release. Limitations included a small number of high-quality articles and varied timing of orthotic wearing and exercise protocols. EBP

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References

1. Shen PC, Chou SH, Lu CC, et al. Comparative effectiveness of various treatment strategies for trigger finger by pairwise meta-analysis. *Clin Rehabil.* 2020;34(9):1217-1229. [STEP 1]
2. Lunsford D, Valdes K, Hengy S. Conservative management of trigger finger: a systematic review. *JHT.* 2017;32: 212-221. [STEP 3]

Is cannabidiol an effective treatment of insomnia in adults?

EVIDENCE-BASED ANSWER

Not clear. Cannabidiol may improve some self-reported subjective measures of sleep for patients with insomnia; however, the data are limited to small, low-quality studies (SOR: **C**, systematic review of a small cohort and a case series and a cross-sectional cohort).

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A recent systematic review from 2020 investigated cannabinoid therapies for various sleep disorders. The review included 14 preclinical studies and 12 clinical studies (N=250). We found no published randomized controlled trials of cannabinoids in clinician-diagnosed insomnia. Only two studies specifically addressed cannabidiol (CBD) for insomnia in adults. One retrospective study (n=72) looked at self-administered 25 to 75 mg oral capsules CBD for psychiatric patients diagnosed with a sleep or anxiety disorder, with exclusion of patients with primary diagnosis of schizophrenia, post-traumatic stress disorder, or agitated depression. Sleep improvement was evaluated by Pittsburgh Sleep Quality Index (PSQI), which is a self-reported measure that assesses sleep quality based on a 19-item questionnaire. PSQI has a maximum score of 21 and higher scores equate to worse sleep. Mild improvement in sleep was seen in the sleep disorder group (n=25) evidenced by decreased PSQI (baseline 13.08-9.33 after 3 months). Another small study looked at oral capsule CBD (40, 80, and 160 mg) versus placebo and a control (nitrazepam 5 mg) in healthy adult volunteers complaining of sleep difficulties. CBD was taken 30 minutes before bed, and self-reported increase was noted in sleep duration (two-thirds of patients reported sleeping >7 hours, $P \leq .05$ over baseline) in the group receiving 160 mg CBD. However, the study was a small sample (n=15) of researcher family members with subjective complaints of poor sleep and was measured with a nonvalidated 10-question sleep questionnaire. Limitations of this systematic review included English-only articles, small sample sizes, poor methodological quality, and high risk of bias.

One longitudinal cross-sectional study investigated cannabis use for anxiety and insomnia. One hundred fifty-two regular users, 21 to 70 years old, with mild anxiety disorders (Generalized Anxiety Disorder-7 score 5 or more) were surveyed using the PSQI. Regular use was defined as use of smoking, vaporization, or edible consumption at least once per week. Regression analysis was used to determine association between sleep and cannabis use, and *P*-values were adjusted for multiple variables, including age and amount of cannabis use. β co-efficient reflects the strength of the effect of cannabis use on different variables, with higher values indicating a stronger effect. Self-reported current use and more days of cannabis use were associated with increased expectation of improved sleep ($\beta=0.03$, $P=.04$). However, this was associated with worse subjective sleep quality ($\beta=1.34$, $P=.02$). This study was limited because of the sample being primarily white women with comorbid anxiety disorders. Tetrahydrocannabinol (THC)/CBD concentrations were self-reported increasing risk for recall bias, and THC's psychoactive properties may have had an impact. In addition, cross-sectional design limits the strength of evidence. EBP

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References

1. Suraev AS, Marshall NS, Vandrey R, et al. Cannabinoid therapies in the management of sleep disorders: a systematic review of preclinical and clinical studies. *Sleep Med Rev.* 2020;53:101339. [STEP 3]
2. Winiger EA, Hitchcock LN, Bryan AD, Cinnamon Bidwell L. Cannabis use and sleep: expectations, outcomes, and the role of age. *Addict Behaviors*. 2021;112(5):106642. [STEP 3]

Is cervical cancer screening with high-risk human papillomavirus testing superior (or at least as accurate) at detecting CIN3+ compared with screening with cytology?

EVIDENCE-BASED ANSWER

Yes. Cervical cancer screening with high-risk human papillomavirus (HPV) alone increases detection of grade 3 cervical intraepithelial neoplasia or worse (CIN 3+) compared with cytology alone (SOR: **A**, systemic review and retrospective cohort trial). Experts do not agree on the preferred method for cervical cancer screening but state that for women 30 to 65 years old, either HPV testing alone every five years or cytology alone every three years is acceptable (SOR: **C**, practice guidelines and recommendations).

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A 2018 systematic review addressing the benefits and harms of cervical cancer screening using high-risk human papillomavirus (hrHPV) testing included eight RCTs comparing cytology with either cotesting (ie, hrHPV plus cytology; 4 trials, N=127,717) or hrHPV alone (4 trials, N=282,839).[1] The trials were from Australia, Canada, Finland, Italy, the Netherlands, Sweden, and the United Kingdom, ranging in size from 4,995 to 203,425 women. Patients were between 20 and 65 years old and underwent one or two rounds of screening at intervals ranging from 2.5 to 5 years. Follow-up ranged from 4 to 9 years. HPV assays used were Hybrid Capture 2 (HC2) (5 trials), glycoprotein 5+/6+ polymerase chain reaction enzyme immunoassay (2 trials), and either HC2 or Cobas 4,800 (1 trial). Cytology was either conventional (4 trials) or liquid based (4 trials). Due to the rarity of invasive cervical cancer in the countries where the trials were located, the primary outcome was grade 3 cervical intraepithelial neoplasia or worse (CIN 3+) at the first round of screening. Indications for further assessment (ie, colposcopy) to diagnose CIN 3+ varied and included a positive HPV assay result, atypical squamous cells of undetermined significance (ASCUS), and low-grade or high-grade squamous intraepithelial lesions. CIN 3+ was detected in as few as 0.1% and as many as 1.6% of women in the studies. Primary hrHPV screening had an increased rate of CIN3+ detection compared with cytology alone at the first screening (relative risk [RR] range, 1.6 [95% CI, 1.1–2.4] to 7.5 [95% CI, 1.0–54]). No studies showed higher detection of CIN3+ with cotesting versus cytology after two screening rounds (RR range 0.96 [95% CI, 0.74–1.2] to 1.3 [95% CI, 0.92–1.9]). False-positive rates were higher with HPV versus cytology (6.6%–7.4% vs 6%–6.5%, respectively) and with cotesting versus cytology (5.8%–19.9% vs 2.6%–10.9%, respectively). The quality of the studies was fair to good. Limitations included heterogeneity in screening, protocols, and follow-up. Randomizations was also not maintained for more than one to two rounds of screening.

A 2017 retrospective cohort study compared the relative performances of HPV testing and cytology in identifying cervical cancer and precancer prior to the diagnosis.[2] Researchers reviewed the medical records from a large integrated health care organization in the United States for approximately 1.2 million women of 30 years old and older who underwent cervical cotesting at 3-year intervals. Patients with abnormal cytology were referred for colposcopy; patients with positive HPV and negative cytology or negative HPV and ASCUS cytology were retested in one year. Precancers were defined as CIN 3 and adenocarcinoma in situ. For identifying cancer, the sensitivities were 77% for HPV testing versus 59% for cytology ($P<.001$); for precancer, the sensitivities were 84% for HPV testing versus 62% for cytology ($P<.001$).

A 2018 US Preventive Services Task Force recommendation statement concluded that for women 30 to 65 years old, screening for cervical cancer should be done with cytology alone every three years, hrHPV testing alone every five years, or cotesting with both modalities every five years (grade A recommendation indicating a high certainty that the net benefit is substantial, based on consistent results from well-

designed and well-conducted studies with primary care patients).[3]

A 2020 consensus guideline from the American Cancer Society recommended screening women 25 to 65 years old for cervical cancer using HPV testing alone every five years. Cotesting every five years or cytology alone every three years was considered acceptable where access to US Food and Drug Administration–approved primary HPV testing was not available (strong recommendation based on a review of evidence-based literature and expert opinion).[4]

A 2016 practice bulletin from the American College of Obstetricians and Gynecologists (ACOG) stated that for women 30 to 65 years old, the preferred screening was cotesting with cytology and hrHPV every five years, while cytology alone every three years was acceptable (level A recommendation based on good and consistent scientific evidence).[5] For women 25 years old and older, ACOG indicated that hrHPV alone could be considered instead of cytology alone (level B recommendation based on limited and inconsistent scientific evidence). The practice bulletin was developed by a committee and was based on both scientific evidence and expert opinion. EBP

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References

1. Melnikow J, Henderson JT, Burda BU, Senger CA, Durbin S, Weyrich MS. Screening for cervical cancer with high-risk human papillomavirus testing: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;320(7):687-705. [STEP 1]
2. Schiffman M, Kinney WK, Cheung LC, et al. Relative performance of HPV and cytology components of cotesting in cervical screening. *J Natl Cancer Inst*. 2018;110(5):501-508. [STEP 4]
3. US Preventive Services Task Force; Curry SJ, Krist AH, Owens DK, et al. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320(7):674-686. [STEP 1]
4. Fontham E, Wolf A, Church T, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin.* 2020;70(5):321-346. [STEP 5]
5. Practice Bulletin No. 168 Summary: cervical cancer screening and prevention. *Obstet Gynecol.* 2016;128(4):923-925. [STEP 5]

Do energy drinks increase blood pressure in adults without the diagnosis of hypertension?

EVIDENCE-BASED ANSWER

For several hours after consumption of commercial energy drinks, diastolic blood pressure increases (range of 2.2–7.0 mmHg). Systolic blood pressure inconsistently increases by up to 4.4 mmHg (SOR: **C**, meta-analysis of randomized controlled trials [RCTs] and 2 additional small RCTs).

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A 2016 meta-analysis of 15 randomized controlled trials (RCTs; 14 crossover and 1 parallel design, N=340) studied the relationship between energy drinks and blood pressure.[1] Participants had no preexisting hypertension and ranged from 18 to 40 years old, aside from one study that included participants as young as 15 years old (n=40). Participants drank energy drinks with 80 to 230 mg of caffeine per drink when caffeine amounts were reported. Participants in the control groups consumed various placebo drinks, with the exception of two studies where the control group drank a caffeinated beverage that was not an energy drink, and two other studies where participants drank decaffeinated energy drinks. Systolic blood pressure, diastolic blood pressure, and heart rate were monitored at 30 minutes to up to six hours after drink consumption. Compared with baseline measurements, participants who consumed a caffeinated energy drink had an increase in systolic blood pressure of 4.4 mmHg (15 trials, N=340; 95% CI, 2.7–

6.2) and increase in diastolic blood pressure of 2.7 mmHg (14 studies, N=322; 95% CI, 1.5–4.0). Subgroup analysis showed a greater systolic blood pressure increase with caffeine content >200 mg (7 studies, N=112; mean difference [MD] 6.44 mmHg; 95% CI, 4.62–8.27) than with caffeine <200 mg (5 studies, N=155; MD 3.72 mmHg; 95% CI, 1.7–5.75). No control was present for baseline participant caffeine consumption.

A 2019 crossover double-blinded RCT (n=38), not included in the above meta-analysis, investigated the effects of energy drinks and their active components (caffeine and taurine) on a variety of cardiometabolic effects, including blood pressure.[2] Participants were healthy German students, 19 men and 19 women, ages 18 to 25 years old, body mass indexes ranging from 20 to 25 kg/m^2, with no past medical history, including hypertension. Participants were excluded if they were taking any medications aside from contraceptives or if they had habitual consumption greater than one cup per day of coffee, 60 g alcohol per week in men or 30 g for women, or 500 mL per week of energy drinks. Participants were assigned into one of two sample volume groups (750 and 1,000 mL) and consumed four products at the assigned volume: Red Bull® energy drink (80 mg caffeine/250 mL, also contains taurine), control product (commercial sports drink), control product + caffeine (32 mg/100 mL), and control product + taurine (400 mg/100 mL). Participants consumed 250 mL of the drink every 15 minutes for a total of 45 minutes or one hour to consume the full allocated volume. Blood pressure was taken before administration of the drink samples and again at one hour and three hours after beverage consumption. This was repeated with a washout period of four days until data were collected on all four study products. No significant difference was noted in blood pressure between the 750 and 1,000 mL volume groups across all four study products, so data were pooled between the two groups when looking at blood pressure changes. Overall, the energy drink elevated blood pressure measurements at one hour compared with baseline measurement: systolic blood pressure by 3.9 mmHg ($P<.001$) and diastolic blood pressure by 2.2 mmHg ($P<.001$). At one hour, the control product plus caffeine also increased systolic blood pressure by 3.8 mmHg and diastolic blood pressure by 2.2 mmHg (both P values$<.05$). Blood pressure returned to baseline by the 3–hour mark. Significant study limitations included the small sample size and questionable generalizability given both the relatively good health of participants and the large volume of energy drink consumed. The study also excluded patients who consume moderate amounts of coffee and energy drinks, which could create a confounder to the results.

A 2018 RCT (n=68), not included in the above meta-analysis, compared the effect of energy drink versus water consumption on blood pressure, heart rate, and blood glucose in a group of healthy Polish college students.[3] Mean age of participants was 25 years old and they were 78% female. Participants were excluded if they had cardiovascular disease, diabetes, chronic health conditions, consistent alcohol use, were pregnant/lactating women, or those taking any medications with potential to exert cardiovascular effects. Participants in the experimental group were instructed to drink one 250-mL energy drink per hour for three hours (total volume 750 mL). Each drink was noted to contain 80 mg of caffeine. Systolic and diastolic blood pressures were measured before beverage consumption as well as 30 minutes and one hour after the completion of each of the three beverages. A similar protocol was followed for the control group where participants consumed the same volume of water. No statistically significant increase was noted in systolic blood pressure compared with baseline after consumption of three energy drinks; however, an 8% increase was noted in diastolic blood pressure compared with baseline (76 mmHg preconsumption vs 83 mmHg postconsumption, $P<.003$). The control group did not experience any significant increases in blood pressure. The overall good health of its volunteers is a potential limitation in the generalizability of this study. EBP

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References

1. Shah SA, Chu BW, Lacey CS, Riddock IC, Lee M, Dargush AE. Impact of acute energy drink consumption on blood pressure parameters: a meta-analysis. *Ann Pharmacother.* 2016;50(10):808-815. [STEP 1]

2. Basrai M, Schweinlin A, Menzel J, et al. Energy drinks induce acute cardiovascular and metabolic changes pointing to potential risks for young adults: a randomized controlled trial. *J Nutr*. 2019;149(3):441-450. [STEP 2]
3. Nowak D, Gośliński M, Nowatkowska K. The effect of acute consumption of energy drinks on blood pressure, heart rate and blood glucose in the group of young adults. *Int J Environ Res Public Health*. 2018;15(3):544. [STEP 2]

Is melatonin safe to use long term?

EVIDENCE-BASED ANSWER

Most likely. No apparent differences are observed in adverse effects of daily melatonin (2 mg) use in adults after 29 weeks compared with placebo. Adverse effects of long-term melatonin use in adults are mild, without clinically relevant differences between melatonin and placebo (SOR: **B**, randomized controlled trial). In children, there do not appear to be negative impacts of daily melatonin use (mean 2.5 mg) on development or mental health after several years of usage (SOR: **B**, case–control study).

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A randomized controlled trial (n=791) investigated whether the efficacy of prolonged release melatonin (PRM) observed in short-term studies is sustained during continued treatment in adult outpatients (aged 18–80 years old).[1] All patients had primary insomnia by Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, criteria with sleep latency longer than 20 minutes. The intervention group received PRM 2 mg orally two hours before bedtime for 29 weeks and the control group received placebo. Investigators recorded the incidence and type of adverse events (AEs) and the results of clinical laboratory tests, vital signs, electrocardiograms (EKGs), and physical examination. Additional outcomes were withdrawal effects after stopping PRM. No formal statistical testing was performed on any safety data. PRM and placebo patients had similar rates of any AE during the run-in (35.9% vs 34.5%, respectively) and extension periods (76.8% vs 73.8%, respectively). No apparent differences were observed between groups in vital signs, EKG, physical examination, and any measured safety outcomes. The most commonly reported AEs in both the PRM- and the placebo-treated groups were mild and included nasopharyngitis, arthralgia, diarrhea, lower and upper respiratory tract infections, and headache.

A small prospective case–control study examined the impact of long-term melatonin use on pubertal development, sleep quality, and mental health in children.[2] Patients were children who had previously participated in a melatonin dose-finding trial conducted between 2004 and 2007—Dutch children ages 6 to 12 years old with chronic sleep-onset insomnia and average sleep-onset latency greater than 30 minutes. In 2008, investigators sent questionnaires to all 69 children who completed the dose-finding trial and used melatonin longer than 6 months. Questionnaires asked for data on demographics, melatonin use, mental health, sleep habits, and pubertal development. The primary safety outcomes were the Strengths and Difficulties Questionnaire (SDQ) score and Tanner scores. Secondary outcomes were persistent use of melatonin, mean effective dose, adverse events, and menarche/oligarche related to parental menarche/oligarche. The SDQ included 25 questions that measured negative and positive behavioral and emotional attributes related to emotional symptoms, conduct problems, hyperactivity attention, peer relationships, and prosocial behaviors. Forty-eight participants continued to use melatonin after a mean of 3.1 years (min 1.0 to max 4.6 years). Eight percent had discontinued therapy after 4 years for various reasons, including loss of response, apathy, weight gain, and recommendation of a general practitioner. Case mean SDQ scores and Tanner scores were indistinguishable from controls. Reported adverse effects included nausea (one child), apathy and weight gain (one child), nocturnal diuresis (three children), and headache (21 children at least monthly, 11 less than monthly). Limitations of this study include lack of blinding, small sample size, geographic limitation, medication-free intervals during the holidays, recall bias, and low response rates to some items of the questionnaires. EBP

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References

1. Wade AG, Ford I, Crawford G, et al. Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: a randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety. *BMC Med.* 2010; 8(1):51. [STEP 1]
2. van Geijlswijk IM, Mol RH, Egberts TC, et al. Evaluation of sleep, puberty and mental health in children with long-term melatonin treatment for chronic idiopathic childhood sleep onset insomnia. *Psychopharmacology*. 2011;216(1):111-120. [STEP 2]

Do parent training programs reduce crying time in infants with and without colic?

EVIDENCE-BASED ANSWER

Parental training programs may reduce crying time in infants with colic by about two hours per day (SOR: **B**, systematic review of low-quality randomized controlled trials [RCTs]). In a general population of infants without a diagnosis of colic, parental programs do not seem to reduce total daily crying time but may slightly reduce inconsolable crying by about four minutes (SOR: **C**, small RCT).

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A 2019 systematic review and meta-analysis of six randomized controlled trials (RCTs) (N=286 infants) examined the effectiveness of parental training programs on infant colic.[1] Four trials were from the United States (N=216), and one each was from Canada (N=22) and Iran (N=48); all were published between 1988 and 2013. Participants were parents of infants between two weeks and three months old (the mean ages ranged between 5.1 and 7.2 weeks old) with infantile colic, either diagnosed by a pediatrician or meeting criteria of a minimum of three hours of crying, three days per week, for three weeks. The included trials examined various parental training programs incorporating individualized parental counseling sessions given by clinicians, nurses, or therapists, in the home or clinic, through in-person or telephone visits. In addition to counseling, the programs provided educational materials (written, video, or worksheets) or tools (blankets or pacifiers). The sessions' content focused on instructing parents on how to effectively respond to infant cues (eg, need to be fed, held, stimulated, or go to sleep), teaching techniques for soothing such as skin-to-skin contact between the mother and the infant ("kangaroo care"), and providing parental reassurance, empathy, and support. Interventions were between 6 days and 6 weeks duration; only one home-based trial specifically indicated an intensity of four one-hour sessions. The control groups received usual care, advice to rock their infant, or empathy and supportive statements from researchers in all but one trial, where the control group received hydrolyzed formula and counseling on dairy-exclusion. Parent-reported crying time, measured as minutes or hours per day at the end of the intervention, was a primary outcome. Pooled results demonstrated that parent training was associated with a large reduction in daily crying time compared with control (3 RCTs, N=157; mean difference [MD] –114 min/d; 95% CI, –144 to –83 min/d). Results from three RCTs could not be pooled. One RCT (n=48) comparing instructions to mothers to provide two hours per day of kangaroo care versus advice to rock their infant showed after seven days a decline in baseline daily crying from a mean of 3.5 hours in both the groups to 1.7 hours in the intervention group versus three hours in the control group ($P<.05$). A second trial (n=61) evaluating family-centered parent training versus a brief office visit reported a 3.1-hour reduction in daily crying from baseline to six weeks (–64%; 95% CI, –60% to –69%) in the intervention group compared with a 0.97-hour decline (–27%; 95% CI, –24% to –30%) over six weeks in the control group. A third RCT (n=20) found a significant reduction in daily crying time from baseline to 7 to 9 days comparing parental counseling with formula and dairy-exclusion counseling (intervention group MD –2.1 h/d vs control group MD –1.2 h/d, $P<.02$). The reviewers graded the evidence quality as low, primarily because of the lack of blinding (of parents to the intervention and of the outcome assessment), as well as unclear allocation concealment in most studies and low patient numbers in the trials.

A 2019 pilot RCT (n=36 infants) examined the effectiveness of a specific parent training intervention called Baby Triple P (BTP) in a general population of infants to improve parenting experiences and infant crying, feeding, and sleeping.[2] Participants were highly educated, partnered parents living in Germany with an average age of 34 years old; the trial excluded mothers with medical pregnancy complications. The intervention group received training by a BTP-certified psychologist who led eight one-hour sessions (4 group sessions before birth and 4 telephone sessions after birth) that included education on positive parenting, responding to the baby, survival skills, partner support, and implementing parenting routines. The control group received care as usual. The primary outcomes were total daily crying and inconsolable crying times (the latter defined as crying spells that occurred unpredictably, for no obvious reason, and described as colic or excessive crying) measured at six months after birth. No difference was observed in total daily crying time at six-month follow-up in the parent training versus control groups (12 vs 25 minutes; MD –13 minutes; $P=.09$); however, parent training was associated with a small reduction in daily inconsolable crying time at six months (0 vs 3.6 minutes; MD –3.6 minutes; $P=.04$) when compared with care as usual. This RCT was limited by the lack of blinding of the parents and researchers, measurement outcomes that were parent-reported, and unclear methods of randomization and allocation concealment. EBP

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References

1. Gordon M, Gohil J, Banks SS. Parent training programmes for managing infantile colic. *Cochrane Database Syst Rev*. 2019;12(12):CD012459. [STEP 2]
2. Popp L, Fuths S, Schneider S. The relevance of infant outcome measures: a pilot-RCT comparing baby triple P positive parenting program with care as usual. *Front Psychol*. 2019;10:2425. [STEP 3]

Does parental education on screen time recommendations lead to reduced screen time in pediatric patients?

EVIDENCE-BASED ANSWER

Parental education results in modestly reduced screen time for children two to six years old (SOR: **A**, meta-analysis of randomized controlled trials [RCTs] and single RCT). The optimal setting, mode of delivery, and duration of sessions all remain unclear.

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A 2018 meta-analysis of 17 randomized controlled trials (RCTs; N=4,261) evaluated a variety of interventions to reduce screen time in children with mean ages of five years old or younger.[1] Children not yet in primary or elementary school were recruited from preschools, childcare centers, primary care offices, and community-based settings. Interventions varied from a one-time educational session to seven phone or face-to-face sessions with mailed educational information over 24 months. Educational materials focused on screen time recommendations, increasing physical activity, and other healthy lifestyle changes. Control groups received usual care or no intervention. The primary outcome was reduction in screen time. After pooling of all 17 trials, a significant reduction was noted in screen time per day between the intervention groups and the control groups (mean difference [MD] –17 minutes per day, $P<.01$; $I^2=89\%$). The most effective interventions for screen time reduction had a duration of greater than six months (6 trials, N not given; MD –16 minutes per day, $P<.0001$) and were conducted in a home setting (4 trials, N not given; MD –31 minutes per day, $P=.01$). This meta-analysis was limited by the heterogeneity of results, variation in reporting of results, and inability to adjust for confounding factors.

A 2020 RCT (n=141) investigated the effectiveness of group-based parental education on screen time in children from Taiwan.[2] Dyads of children four to six years old with screen time of greater than two hours per day and at least one parent over 20 years old living at home with the child were recruited from 14 private kindergartens. Parent–child dyads with children with chronic diseases, hearing impairment, or neurological conditions were excluded. Parents in the intervention group received eight weekly, 50-minute sessions meant to increase knowledge and self-efficacy about screen-use through reflection, group discussions, and role-play activities. The control group received no education. The primary outcome was parent-reported screen time after eight weeks. After eight weeks, screen time in the intervention group was significantly reduced compared with baseline (MD –68 minutes per day, $P<.0001$). The control group had no change in screen time versus baseline. One key limitation was social desirability bias, as parents self-reported screen time and had knowledge of the goal to reduce screen time. EBP

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References

1. Downing KL, Hnatiuk JA, Hinkley T, Salmon J, Hesketh KD. Interventions to reduce sedentary behaviour in 0-5-year-olds: a systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med.*. 2018;52(5):314-321. [STEP 1]
2. Lin YM, Kuo SY, Chang YK, et al. Effects of parental education on screen time, sleep disturbances, and psychosocial adaptation among Asian preschoolers: a randomized controlled study. *J Pediatr Nurs.*. 2021;56:e27-e34. [STEP 2]

Does a course of cognitive behavioral therapy reduce the recurrence of depression in patients on antidepressants?

EVIDENCE-BASED ANSWER

Introduction of sequential cognitive behavioral therapy (CBT) in combination with antidepressant medication (ADM) or undergoing CBT alone after acute intervention with ADM reduces depression recurrence compared with maintenance therapy with ADM alone (SOR: **A**, meta-analysis of randomized controlled trials [RCTs] and 1 RCT). Patients with three or more previous major depressive episodes may benefit from preventative CBT (SOR: **B**, single RCT).

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A 2016 meta-analysis of 13 randomized controlled trials (RCTs; N=1,410) examined the effectiveness of cognitive behavioral therapy (CBT) in adults with major depressive disorder after acute-phase intervention with pharmacotherapy at reducing relapse/recurrence.[1] Investigators defined relapse/recurrence using the normative values on depression diagnostic tools (DSM-IV, DSM-III-R, or Spitzer's Research Diagnostic Criteria). The trials included 68.5% female patients, average age 45 years old, who were partially or fully remitted after treatment with ADM in the acute phase. Patients <18 years old, those treated through internet or telephone, who used CBT before pharmacotherapy, or who had psychiatric disorders other than MDD were excluded. Multiple forms of in-person CBT (eg, mindfulness-based and group CBT) were included in the analysis. Control groups included usual treatment with referring entity, clinical monitoring of medication, or interventions like journaling or exposure strategies. CBT in sequence with post-acute pharmacotherapy for 8 to 32 weeks significantly decreased relapse/recurrence of depression compared with controls (13 trials, N=1,410; pooled risk ratio [RR] 0.78; 95% CI, 0.67–0.91; number needed to treat [NNT]=8). In a subanalysis comparing sequential treatment with CBT plus ADM continuation versus ADM continuation or treatment as usual alone (defined as standard care typically provided by providers, non-exclusive of ADM), the CBT group had a significant decrease in relapse/recurrence of depression in follow-up periods ranging from 28 weeks to 6 years (9 trials, N=1,151; RR 0.81; 95% CI, 0.69–0.96; NNT=10). In addition, patients treated sequentially with CBT alone after tapering and discontinuation of ADM had

significantly lower rates of relapse/recurrence of depression, compared with those with ADM continuation or clinical management alone in follow-up periods ranging from 15 months to 6 years (4 trials, N=179; RR 0.67; 95% CI, 0.48–0.94; NNT=5). Limitations included publication bias, variation in sample sizes, duration of treatments, and medication dosages.

A 2020 RCT (n=292) evaluated long-term treatment outcomes of combined intervention with CBT and ADM (n=155) versus medication alone (n=137) among adults (average age 45 years old) with chronic major depression (episode lasting for 2 years or longer) or recurrent major depression (any episode following a previous MDD diagnosis).[2] This study was the second of two phases, with phase 1 patients treated with ADM alone (monotherapy) or in combination with CBT. In phase 2, recovered patients from either group were randomly assigned to ADM maintenance or discontinuation. In the ADM monotherapy group (n=137), patients in the ADM maintenance group showed significantly lower rates of recurrence over three years than those in the ADM discontinuation group (48.5% vs 74.8%; hazard ratio [HR] 0.47; 95% CI, 0.29–0.75; NNT=2.8). In the combination therapy group (ADM+CBT; n=155), patients in the ADM maintenance group showed significantly lower rates of recurrence compared with the ADM discontinuation group (48.5% vs 76.7%; HR 0.46; 95% CI, 0.30–0.71; NNT=2.7). Analysis across the two phases noted no significant differences in likelihood of sustained recovery between phase 1 treatments (ADM alone vs in combination with CBT; OR 1.08; 95% CI, 0.52–2.11). Limitations included limited power of study; patients with chronic or recurrent major depression, instead of an initial episode; and no CBT-alone phase 1 treatment group.

A 2015 RCT (n=172) compared the combination of preventive cognitive therapy (PCT) and treatment as usual versus usual care alone (defined as "naturalistic" care with standard pharmacotherapy treatment or no treatment) in the prevention of depression recurrence.[3] PCT included eight weekly two-hour group sessions focusing on identifying patients' negative thought patterns and replacing those with positive memories and other prevention strategies. Patients were White (98% PCT, 99% usual care), female (73% PCT, 74% usual care), average age of 45 years old, with at least two major depressive episodes in the previous five years. Patients were randomized to receive PCT with usual care or usual care alone and were followed for 10 years, with follow-up durations at three, 12, 24, 36, 66, and 120 months to determine time to first recurrence of depression. Secondary outcomes included cumulative frequency of first recurrence, average severity of recurrence, and longitudinal risk of recurrence. Among patients with more than three major depressive episodes, PCT with usual care was shown to have a significant preventive effect in reducing recurrence of depression when compared with usual care alone (HR 0.58; 95% CI, 0.40–0.84). Limitations included a high dropout rate, recall bias because of increase in time between assessments, and use of other treatments during the study period. EBP

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References

1. Guidi J, Tomba E, Fava GA. The sequential integration of pharmacotherapy and psychotherapy in the treatment of major depressive disorder: a meta-analysis of the sequential model and a critical review of the literature. *Am J Psychiatry*. 2016;173(2):128-137. [STEP 1]
2. DeRubeis RJ, Zajecka J, Shelton RC, et al. Prevention of recurrence after recovery from a major depressive episode with antidepressant medication alone or in combination with cognitive behavioral therapy: phase 2 of a 2-phase randomized clinical trial. *JAMA Psychiatry*. 2020;77(3):237. [STEP 2]
3. Bockting CLH, Smid NH, Koeter MWJ, Spinhoven P, Beck AT, Schene AH. Enduring effects of preventive cognitive therapy in adults remitted from recurrent depression: a 10 year follow-up of a randomized controlled trial. *J Affective Disord.* 2015;185:188-194. [STEP 2]

Does circumcision decrease rates of human papilloma virus infection in males?

EVIDENCE-BASED ANSWER

Circumcision is associated with an absolute 8% lower prevalence of human papilloma virus infection in HIV-negative males (SOR: **B**, meta-analysis of cross-sectional studies) and equal prevalence in HIV-positive males (SOR: **C**, cross-sectional analysis). Whether the difference is because of reduced acquisition, increased clearance, or both remains unknown.

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A 2017 systematic review and meta-analysis of 24 trials (5 randomized controlled trials [RCTs]; 19 cross-sectional and cohort studies, N=15,156) evaluated the association between male circumcision and human papilloma virus (HPV) prevalence in HIV-negative men from various continents.[1] The trials included males (ages 15–70 years old); circumcision status was confirmed by physical examination (20 studies) or self-report (4 studies). The primary outcome of HPV infection was assessed through polymerase chain reaction (PCR) assay in most of the studies (20/24). Ten of the 24 trials demonstrated lower HPV prevalence among circumcised males, one trial demonstrated higher prevalence, and 13 did not show any difference. Overall, HPV prevalence was lower among circumcised males (odds ratio [OR] 0.68; 95% CI, 0.56–0.82, number needed to treat=13). Limitations included significant between-study heterogeneity (I^2=70%).

A 2009 study of two RCTs (N=520) conducted in parallel in Rakai, Uganda evaluated the effect of circumcision on the incidence of HPV seroconversion.[2] The trials included HIV-negative, uncircumcised males ranging in age from 15 to 49 years old. The intervention group of 233 males were immediately circumcised and the control group of 287 males were circumcised 24 months later. HPV status was evaluated by PCR assay for high-risk genotypes at baseline and at 24 months. Baseline high-risk HPV rates were similar in each group (38% vs 37%; relative risk [RR] 1.0; 95% CI, 0.79–1.3). At 24 months, high-risk HPV prevalence was lower in the intervention group (18% vs 28%; RR 0.65; 95% CI, 0.45–0.94). Limitations included assessment only at baseline and 24 months, possible self-selecting population, and unknown mechanism of reduced HPV acquisition rate or increased HPV clearance rate.

A 2013 cross-sectional analysis of the Can Ruti HIV-positive Men cohort (N=637) in Spain evaluated the association between male circumcision and the prevalence of penile HPV infection among HIV-infected men.[3] Three populations were analyzed: the entire group, the men who have sex with men (MSM) group, and the heterosexual group. Patients included 167 circumcised and 539 uncircumcised adult males (median age range 40–42 years old) without current or history of HPV-related disease of the anus, penis, or mouth. At the baseline visit, all patients completed a detailed self-administered questionnaire and underwent a clinical inspection of the anus, penis, and mouth, from which samples were collected for detecting HPV infection. A digital rectal examination was also performed. All patients were then monitored annually. Overall, prevalence of any penile HPV infection was similar among circumcised and uncircumcised men (22% vs 27%; OR 0.8; 95% CI, 0.5–1.2; adjusted analysis). Similarly, no difference was found among MSM (22% vs 27%; OR 0.8; 95% CI, 0.5–1.3) or heterosexual men (24% vs 28%; OR 0.8; 95% CI, 0.4–2.0). Results of this study were limited by its cross-sectional design, small sample size of circumcised heterosexual HIV-infected men, and overall lower rates of circumcision among European countries than the United States. EBP

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References

1. Zhu YP, Jia ZW, Dai B, et al. Relationship between circumcision and human papillomavirus infection: a systematic review and meta-analysis. *Asian J Androl*. 2017;19(1):125-131. [STEP 2]

2. Tobian A, Serwadda D, Quinn T, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *New Engl J Med.* 2009;360(13):1298-1309. [STEP 2]
3. Canadas MP, Darwich L, Videla S, et al. Circumcision and penile human papillomavirus prevalence in human immunodeficiency virus-infected men: heterosexual and men who have sex with men. *Clin Microbiol Infect*. 2013;19(7):611-616. [STEP 4]

Is screening for vitamin D deficiency indicated in asymptomatic adults living at high latitudes?

EVIDENCE-BASED ANSWER

While screening for vitamin D deficiency is recommended in high-risk groups, those living at high latitudes are not identified as one of these groups (SOR: **C**, evidence-based guideline). However, it may be reasonable to treat, without screening, asymptomatic individuals who live in high latitudes (SOR: **C**, evidence-based guideline).

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In 2014, the U.S. Preventive Services Task Force (USPSTF) reviewed 27 studies (26 randomized controlled trials and one cohort study) that focused on community-dwelling, nonpregnant adults who were 18 years old or older.[1] Patients included those with low vitamin D intake, little or no sun exposure (because of high latitude, long winter seasons, and physical sun avoidance), and decreased vitamin D absorption. Patients with osteopenia, increased fall risk, prediabetes, heart failure, and tuberculosis were excluded. The review found that the accuracy of vitamin D deficiency screening tests was questionable due in part to difficulty in accurately measuring total serum 25-(OH) vitamin D levels, the accepted marker of vitamin D status. The USPSTF concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency (serum vitamin D <20 ng/mL) in asymptomatic adults (lack of bone pain and tenderness, fractures, muscle weakness, and difficulty walking; USPSTF Grade I statement: insufficient).

In a 2011 systematic evidence-based guideline, the Endocrine Society's Clinical Guidelines Subcommittee reviewed 143 articles (including 2 articles from above) and published recommendations based on the findings of a task force formed to inform its recommendations regarding vitamin D deficiency.[2] After completion of two systematic reviews, the task force recommended that individuals who are at risk of vitamin D deficiency (serum 25-(OH) vitamin D <20 ng/mL) should be screened, but population screening of individuals who are not at risk of deficiency is not recommended (1|⊕⊕⊕⊕ = strong recommendation with high-quality evidence). Individuals living at high latitudes were not among the listed population groups considered to be at high risk of deficiency. Nevertheless, the task force concluded that there are "arguments for supplementation [without screening], especially for people living above the 33° latitude," because it is "difficult, if not impossible" to obtain adequate amounts of vitamin D from dietary sources when unprotected sun exposure is limited. EBP

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References

1. LeFevre ML; U.S. Preventive Services Task Force. Screening for vitamin D deficiency in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015;162(2):133-140. [STEP 5]
2. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline [published correction appears in J Clin Endocrinol Metab. 2011 Dec; 96(12):3908]. *J Clin Endocrinol Metab*. 2011;96(7): 1911-1930. [STEP 5]

Does daily application of sunscreen reduce the risk of skin cancer?

EVIDENCE-BASED ANSWER

Likely yes. Daily application of topical sun protection factor (SPF)-16 sunscreen for 4.5 years likely reduces the incidence of squamous cell carcinoma by 3.4% (number needed to treat [NNT] = 29) and invasive melanoma by 1% (NNT=100) at 8- and 10-year follow-ups, respectively, when compared with discretionary use. Daily application of SPF-16 sunscreen does not likely reduce the incidence of basal cell carcinoma at the 8-year follow-up. (SOR: **B**, a single randomized controlled trial with 2 long-term follow-up analyses).

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A 2006 randomized controlled trial (RCT; n=1,621) compared the efficacy of daily application of sun protection factor (SPF)-16 sunscreen versus discretionary use of sunscreen on reducing the incidence of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).[1] The study included residents of Nambour in southeast Queensland, Australia, 25 to 75 years old (female: 56%, fair skinned: 55%, average age: 48.7 years). Patients in the intervention group applied SPF-16 sunscreen every day to their head, neck, arms, and hands for 4.5 years. Compliance was assessed through the measured weight of all returned sunscreen bottles as recorded every three months, and the patients completed questionnaires in the third and fifth years of the trial, in which they reported their average frequency of sunscreen use in a normal week and their use of other sun protection strategies. The primary outcome was the incidence of BCC and SCC at baseline and then every two years for eight years. Diagnosis was made by a full skin examination performed by dermatologists who were blinded to the treatment and control groups and histologic confirmation. Of those assigned to the intervention group, 75% used sunscreen at least three or four days per week. Of those in the control group, 74% used sunscreen no more than two days per week. In an intention-to-treat analysis, sunscreen use was associated with a 38% reduction in the incidence of SCC versus discretionary use (risk ratio, 0.62; 95% CI, 0.38–0.99; absolute risk reduction [ARR]=3.4%; number needed to treat [NNT]=29). No significant difference was observed in the incidence of BCC between the two groups. Limitations included an 8.5% dropout rate.

A 2011 RCT (n=1,446) using the same study participants as the 2006 study with the same inclusion/exclusion criteria and intervention/comparison groups compared the efficacy of daily application of SPF-16 sunscreen versus discretionary use on reducing the primary incidence of melanoma and subtypes.[2] The primary and secondary outcomes were the incidence of melanoma and Clark level of invasion, respectively. Clark levels were defined as follows: Level 1, in situ; Level 2, tumor invasion of papillary dermis; Level 3, tumor extending to the papillary dermis/reticular dermis interface; Level 4, tumor invasion of reticular dermis; and Level 5, tumor invasion of fat. Data were obtained by patient surveys and cross-checked with the Queensland Cancer Registry. At the 10-year follow-up, an intention-to-treat analysis noted daily sunscreen use reduced the incidence of invasive melanoma (Clark levels 2–4) by 73% compared with discretionary use (hazard ratio [HR], 0.27; 95% CI, 0.08–0.97; ARR=1%; NNT=100). However, no significant reduction was observed in the primary incidence of melanoma (HR 0.50; 95% CI, 0.24–1.02). Limitations included an overall higher incidence of BCC and SCC in this study population than that of Australians overall, likely because of more intense monitoring as well as participants being predominately White and living in a condition of extreme ambient UV radiation. EBP

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References

1. van der Pols JC, Williams GM, Pandeya N, Logan V, Green AC. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. *Cancer Epidemiol Biomarkers Prev*. 2006;15(12):2546-2548. [STEP 2]
2. Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. *J Clin Oncol*. 2011;29(3):257-263. [STEP 2]

Does prenatal exercise decrease the incidence of gestational hypertension?

EVIDENCE-BASED ANSWER

Moderate-intensity exercise interventions performed as little as 75 minutes per week in pregnancy can decrease the incidence of gestational hypertension (SOR: **A**, 1 meta-analysis of randomized controlled trials [RCTs] and single RCT).

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A 2018 meta-analysis of 32 randomized controlled trials (RCTs; N=9,648) assessed the effect of exercise on the incidence of gestational hypertension.[1] A subsection of 22 trials (N=5,316) specifically examining exercise-only interventions was identified. Gestational hypertension was defined as diastolic blood pressure ≥90 mmHg on at least two measurements at or later than 20 weeks' gestation. Women were in any trimester of pregnancy and those with multifetal pregnancy, preeclampsia, or contraindications to exercise were excluded. Diverse types of exercise included walking, swimming, cycling, water gymnastics, resistance training, stretching, yoga, or pelvic floor muscle training. Control groups were usual care or no instruction to exercise. The frequency and duration of exercise ranged from 1 to 7 days per week and from 10 to 90 minutes per session. After pooling of the 22 trials, women who exercised had lower odds of gestational hypertension than control groups (odds ratio [OR] 0.61; 95% CI, 0.43–0.85). Women need to participate in at least 23.5 minutes of moderate-intensity exercise at least 3.1 days per week to attain a clinically meaningful reduction in the incidence of gestational hypertension. Subgroup analyses examining different frequency, intensity, duration, volume, and type of exercise found no differences in incidence.

A 2016 RCT (n=840) evaluated the impact of a supervised exercise program during pregnancy on the incidence of pregnancy-induced hypertension.[2] Although included in the meta-analysis described above, this trial illustrated the likely impact of exercise programs when high adherence is achieved. Women had uncomplicated singleton pregnancies defined as absence of diabetes mellitus (type 1, type 2, or gestational) and without history of preterm delivery. Patients were randomized to an exercise intervention group (n=420) and a usual care group (n=420). Supervised exercise sessions occurred three times weekly for approximately 50 minutes and involved aerobic exercise, dance, muscular strength, and flexibility training. The exercise sessions were designed to begin at 9 to 11 weeks of gestation and continue until weeks 38 to 39. After the exclusion of participants who were lost to follow-up or were excluded because of obstetric or personal reasons, a total of 765 pregnant women were available for analysis. Compared with women in the control group, those in the exercise group were less likely to develop gestational hypertension (2.1% vs 5.7%, $P=.009$). Logistic regression analysis controlling for confounding factors, including maternal age, parity, smoking status, prepregnancy body mass index, prepregnancy activity, and occupation, showed that women who did not exercise were three times more likely to develop hypertension during pregnancy (OR 3.0; 95% CI, 1.3–6.8). Adherence in the exercise group was high, defined by the researchers as ≥80% attendance. Limitations included a lack of generalizability because of unusually high adherence rate and a highly sedentary control group. EBP

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References

1. Davenport MH, Ruchat SM, Poitras VJ, et al. Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis. *Br J Sports Med.* 2018;52(21):1367-1375. [STEP 1]
2. Barakat R, Pelaez M, Cordero Y, et al. Exercise during pregnancy protects against hypertension and macrosomia: randomized clinical trial. *Am J Obstet Gynecol.* 2016;214(5):649.e1-649.e8. [STEP 2]

Among adults who are overweight or obese, is fluoxetine effective in decreasing weight?

EVIDENCE-BASED ANSWER

In patients who are overweight or obese, daily fluoxetine at a dose of 60 mg decreases weight by a mean of 2.7 kg during short-term therapy up to six months; however, no clear weight loss is demonstrated when taking fluoxetine at lower doses or over longer periods (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Fluoxetine may increase adverse effects such asthenia, diarrhea, nausea, and sweating compared with placebo (SOR: **C**, conflicting meta-analysis and large RCT).

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A 2019 meta-analysis of 19 randomized controlled trials (RCTs; N=2,216) evaluated the effects of fluoxetine on weight loss.[1] The trials included adults who were overweight or obese and the majority were female. Patients were randomly assigned to receive fluoxetine (n=1,280) at doses of 10 to 60 mg with various comparison groups (n=936) and treated over a period ranging from 3 weeks to 1 year. Most trials compared fluoxetine with placebo, but five trials compared fluoxetine with an anti-obesity agent, no treatment, or omega-3 gel. The primary outcome was mean weight difference at the end of the study. Fluoxetine (across all dosages and durations of treatment) resulted in greater weight loss (10 trials, N=956; mean difference [MD] –2.7 kg; 95% CI, –4 to –1.4) and improved body mass index (BMI; 3 trials, N=97; MD –1.1 kg/m^2; 95% CI, –3.7 to 1.4) compared with placebo. This was driven by fluoxetine 60 mg (7 trials, N=819; MD –2.5 kg; 95% CI, –3.8 to –1.2). Fluoxetine 40 and 20 mg did not result in statistically significant weight loss. Weight loss occurred during a treatment duration of 0 to 3 (5 trials, N=178; MD –3.34 kg; 95% CI, –3.93 to –2.76) and 4 to 6 months (2 trials, N=227; MD –2.75 kg; 95% CI, –3.91 to –1.59) but not at 7 to 12 months. Fluoxetine did not demonstrate any difference versus nonplacebo alternatives (4 trials, N=282) and no treatment (1 trial, n=60). The risk of having at least one adverse event was higher with fluoxetine, although the difference did not reach statistical significance (9 trials, N=1,253; relative risk 1.2; 95% CI, 0.99–1.4; P=.07). The study was limited by overall low-quality evidence, significant heterogeneity among studies in follow-up time, baseline BMI, and fluoxetine dosing as well as by a lack of patient-centered measures such as quality of life and mortality.

A 10-center double-blind RCT (n=458) examined the effectiveness of fluoxetine 60 mg compared with placebo for weight loss.[2] The trial included adults (mean age 43 years old) predominantly female, with an average BMI of 36.2 kg/m^2 in the fluoxetine group and 35.8 kg/m^2 in the placebo group. Pregnant or lactating women and patients who had used an appetite suppressant within two weeks of starting the study were excluded. Patients were randomly assigned to receive fluoxetine 60 mg (n=230) or placebo (n=228) over 52 weeks. The primary outcome of weight difference was assessed during scheduled clinic visits every two weeks for the first eight weeks, every four weeks until week 20, and then every eight weeks until completion of the study at week 52. Patients in both groups were advised on calorie intake reduction and offered an individualized diet at the initial visit. Fluoxetine significantly reduced weight compared with placebo starting at week 2 of therapy and extending to week 28, with the greatest mean weight loss occurring at week 20 (5.1 vs 2.4 kg, $P\leq$.05). The authors reported that patients with BMI ≥40 kg/m^2 demonstrated greater weight loss than those with BMI ≤40 (data not provided). Both groups began to regain weight after 20 weeks and mean weight change at 52 weeks did not differ between the two groups (1.7 vs 2.1 kg, $P\geq$.05). Adverse events documented at regular visits included asthenia, diarrhea, nausea, and sweating and were more frequent and likely to occur in the fluoxetine group (18% vs 8.3%, P=.003). Limitations included heterogeneity among the study sites regarding dietary and behavioral counseling as well as possible confounding with patient–clinician contact time. EBP

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References

1. Serralde-Zúñiga AE, Gonzalez Garay AG, Rodríguez-Carmona Y, Melendez G. Fluoxetine for adults who are overweight or obese. *Cochrane Database Syst Rev*. 2019(10): CD011688. [STEP 1]
2. Goldstein DJ, Rampey AH Jr, Enas GG, Potvin JH, Fludzinski LA, Levine LR. Fluoxetine: a randomized clinical trial in the treatment of obesity. *Int J Obes*. 1994;18(3):129-135. [STEP 2]

What methods increase the completion of advanced directives before hospitalization?

EVIDENCE-BASED ANSWER

Patients are almost twice as likely to complete advanced care directives (ACDs) when physicians discuss ACDs in person with dedicated time and materials necessary to complete the directive during the office visit (SOR: **B**, systematic review not limited to randomized controlled trials [RCTs]). High-intensity interventions, such as oral communication over multiple visits, have the highest association with completion rate (SOR: **B**, meta-analysis not limited to RCTs).

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A 2007 systematic review of 12 randomized controlled trials (RCTs), four prospective trials, and two observational studies (N=22,769) examined various methods for advanced care directive (ACD) completion in the primary care setting.[1] Patients were adults 18 years old and older, most of them were female, and the patients were recruited from Veterans Affairs (VA) clinics, internal medicine residency clinics, and primary care offices. Interventions were categorized as patient-directed interventions (educational materials or social work interventions provided to patients), physician-directed interventions (education or reminders provided to physicians), and combined interventions that implemented both patient and physician interventions. ACD completion rate differences between usual care and intervention groups were reported as effect sizes (ES). After pooling 15 studies, patients exposed to interventions of any kind were significantly more likely to complete an ACD compared with the usual care groups (ES 0.50; 95% CI, 0.17–0.83). Combination interventions were the most successful with an ES above 0.5. Passive education with only educational materials was found to be the least effective with ES of near zero. The most cited barriers to completing ACDs were physicians' lack of time and patients' reluctance to bring up the topic.

A 2008 meta-analysis of 18 RCTs, 27 uncontrolled trials, and 10 nonrandomized trials (N=12,691) assessed characteristics of different interventions to increase completion of ACDs.[2] Patients were adults who were primarily elderly and were seen in the outpatient setting. Interventions were categorized by content (oral information, written information, providing ACD forms, or assistance with forms), main intervener (none specified, team based, or single provider), length (no intervention, single session, or multiple sessions), and intensity (a composite index defined using the content within and length of the intervention). Control groups were defined as no intervention or usual care. The intervention types were then individually analyzed for random effect and then compared with each other for significance of impact on the outcome of reported completed ACDs. Event rates that contained fewer than 30 subjects and duplicate events were excluded from this second analysis, resulting in 120 event rates from 49 studies. The intervention characteristic associated with the highest ACD completion rate was using oral information ($F=21$, $P<.001$) over multiple sessions ($F=14$, $P<.001$), and the intervention characteristic most influential to outcome was intensity of the intervention ($F=29$, $P<.001$). Study limitations included findings of publication bias, inclusion of noncontrolled trials, and 33% of the positive outcome data that were patient-reported rather than verifiably documented. EBP

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References

1. Ramasroop SD, Reid MC, Adelman RD. Completing an advanced directive in the primary care setting: what do we need for success? *J Am Geriatr Soc.* 2007;55(2):277-283. [STEP 1]
2. Bravo G, Dubois MF, Wagneur B. Assessing the effectiveness of interventions to promote advanced directives among older adults: a systematic review and multi-level analysis. *Soc Sci Med.* 2008;67(7):1122-1132. [STEP 1]

Does routine administration of prophylactic antibiotics to newborns delivered through meconium-stained fluid improve neonatal outcomes?

EVIDENCE-BASED ANSWER

No. Among asymptomatic neonates delivered through meconium-stained fluid and neonates with meconium aspiration syndrome, prophylactic antibiotics do not reduce relative risk of neonatal sepsis or neonatal mortality before hospital discharge (SOR: **A**, systemic review of randomized controlled trials [RCTs] and small additional RCT).

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A 2017 systematic review of four randomized controlled trials (RCTs) and quasi-RCTs (N=695) examined the effectiveness of antibiotics for prevention of sepsis within the first 28 days of life in births with meconium-stained amniotic fluid at delivery.[1] Patients were either asymptomatic or meconium aspiration syndrome term and preterm infants. Those with preexisting neonatal sepsis, maternal fever, chorioamnionitis, or prolonged rupture of membranes were excluded. Treatments varied between groups, but all included a standard dose of an aminoglycoside antibiotic and the majority (3 trials) also received a standard dose of a penicillin derivative. Courses varied from 3 to 7 days after birth. The control groups in each of the trials received standard care without antibiotic administration. Sepsis was measured in asymptomatic neonates (1 trial, n=250) and in those with meconium aspiration syndrome (3 trials, N=446). No significant change was observed in risk of sepsis with antibiotic administration compared with usual care in asymptomatic neonates (relative risk [RR] 0.76; 95% CI, 0.25–2.3) or in those with meconium aspiration syndrome (RR 1.5; 95% CI, 0.27–9.0). No difference was observed in neonatal mortality between both treatment groups compared with the usual care infants.

A 2013 single-center RCT (n=69), not included in the above review, studied the effect of antibiotic administration in preventing infection in neonates born through meconium-stained amniotic fluid.[2] Patients were neonates born at a single hospital, through vaginal delivery or cesarean section, and with birth weight between 2,500 and 4,000 g. Women with signs of sepsis or complications during labor or delivery were excluded. Neonates were randomized to receive either a single dose of ampicillin 50 mg/kg IV and gentamicin 8 mg/kg IV (n=34) or standard care without antibiotics (n=35). The primary outcome measured was neonatal infection, based on clinical symptoms or laboratory results at birth and day 3 to 5 of life. Secondary outcomes were neonatal survival at the time of initial hospital discharge. No significant difference was observed between the prophylactic antibiotic group and the standard care group in incidence of neonatal infection (29% vs 23%, $P=.53$) or in neonatal mortality (8.8% vs 2.9%, $P=.30$). Limitations included examination of term infants only, short clinical follow-up, and only using a single dose course of antibiotics. EBP

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References

1. Kelly LE, Shivananda S, Murthy P, Srinivasjois R, Shah PS. Antibiotics for neonates born through meconium-stained

amniotic fluid. *Cochrane Database Syst Rev.* 2017;(6): CD006183. [STEP 1]

2. Kosim MS, Noerpramana NP, Aminullah A, Hadisaputro S. Antibiotics on incidence of infection in neonates with meconium-stained amniotic fluid. *Paediatrica Indonesiana*. 2013;53(1):50-55. [STEP 2]

Does surgery improve outcomes for patients with chronic tennis elbow?

EVIDENCE-BASED ANSWER

Probably not, although it may be a reasonable option if conservative therapy fails. No indication is observed that surgery provides a significant benefit in pain and function when compared with sham and conservative treatments (SOR: **B**, systematic review of small randomized controlled trial [RCTs]). When conservative therapy fails, open and arthroscopic surgery shows improved function and satisfaction equally, with similarly low failure and complication rates (SOR: **B**, meta-analysis of RCTs, cohorts, and a case–control study).

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A 2017 systematic review of 12 randomized controlled trials (RCTs; N=490) examined various treatments aimed at improving function in patients with lateral epicondylitis.[1] Patients were 16 years old and older, approximately equal men and women, who had failed conservative treatment. Owing to issues with heterogeneity among trials, no meta-analysis was performed. A 2016 trial (n=83) compared platelet-rich plasma injection versus surgical release. Function was measured at 12 months using a validated 30-question survey with scores ranging from 0 to 100 (higher scores indicate improvement). No significant difference was observed between improvement in scores between the surgical group and the plasma injection group at 12 months (mean difference [MD] 33 vs 25, P=.37). A 2008 trial (n=62) compared extracorporeal shockwave therapy versus percutaneous tenotomy for pain and function including the "Roles and Maudsley" score. The Roles and Maudsley score is a subjective 4-point assessment of pain and activity. No significant differences were observed between the percentage of patients reporting "good" or "excellent" function in patients treated with shockwave versus surgery at 12 months (62% vs 78%, P=.25). A 2017 trial (n=26) compared open release versus sham surgery over six months. Function was measured through the Orthopedic Research Institute–Tennis Elbow Scoring System, a validated pain and function scoring system which measures the amount of force that can be exerted stressing the lateral epicondyle until pain becomes severe. No difference was observed in mean force improvement between the surgery and sham surgery patients at six months (MD 0.2 vs 0.4 kg, P>.05). Other included trials primarily focused on different forms of injections.

A 2019 meta-analysis of two RCTs, three retrospective cohorts, and one case–control study (N=608) compared the efficacy of open versus arthroscopic debridement in patients who had failed conservative therapy over a period of 1 to 4 years.[2] Patients were a median age of 46 years old and had failed at least six months of conservative therapy for lateral epicondylitis. Patients who did not complete greater than six months of follow-up were excluded. Function was measured through a 0 to 100 scale (higher scores greater improvement) from a validate questionnaire. In the pooled results, no significant difference was observed between open and arthroscopic surgeries in function scores (n=119, MD –1.3; 95% CI, –3.2 to 0.6), failure rate (n=479, odds ratio 0.89; 95% CI, 0.38–2.1), or complications. EBP

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References

1. Bateman M, Littlewood C, Rawson B, Tambe AA. Surgery for tennis elbow: a systematic review. *Shoulder Elbow*. 2019; 11(1):35-44. [STEP 1]

2. Wang W, Chen J, Lou J, Shentu G, Xu G. Comparison of arthroscopic debridement and open debridement in the management of lateral epicondylitis: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2019;98(44):e17668. [STEP 2]

Is spironolactone an effective treatment for adult women with acne?

EVIDENCE-BASED ANSWER

Yes. Spironolactone dosed between 50 and 200 mg/d is associated with improvement in acne among adult women when compared with placebo (SOR: **B**, systematic review of randomized controlled trials [RCTs] with low-quality and retrospective case series). However, spironolactone does not improve acne in combination with combined hormonal contraception when compared with contraception alone (SOR: **B**, systematic review of RCTs with low quality). Spironolactone is not more effective for acne than tetracycline or ketoconazole (SOR: **B**, 1 RCT from systematic review of RCTs with low quality). Spironolactone is not Food and Drug Administration approved for the treatment of acne.

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A 2017 systematic review of 31 studies (N=3,710), consisting of 10 randomized controlled trials (RCTs), 18 case series, and three clinical reports with no clinical outcomes, evaluated the efficacy of spironolactone for acne.[1] Patients were mostly females (proportion not reported in some studies) aged 18 years old and older. All the studies evaluated "improvement of acne" (eg, lesion counts vs acne scores based on different grading systems) as the primary outcome. The RCTs (n=415) compared different types of treatments: spironolactone versus placebo (3 trials), spironolactone versus other antiandrogens, with an oral contraceptive pills (OCPs) in both groups (4 trials), and spironolactone versus ketoconazole with tetracycline (1 trial). Spironolactone treatment varied from 50 to 200 mg daily or divided twice per day for 2 to 12 months compared with placebo (5 trials), cimetidine (3 trials), finasteride (1 trial), ketoconazole (1 trial), tetracycline (1 trial), and flutamide (1 trial; 1 trial had 3 comparators). Four trials included a combined hormonal contraceptive for patients in both the spironolactone and the control groups. In one trial, the spironolactone group was more likely to show at least 50% improvement in number of lesions compared with placebo (18/21 vs 5/21, relative risk [RR] 3.6; 95% CI, 1.64–7.89); the other RCTs comparing spironolactone with placebo did not provide statistical data. Of the trials comparing spironolactone with a combined hormonal contraception to a combined hormonal contraceptive alone, only one trial provided statistical data, showing no difference in acne scores (n=142; RR 1.06; 95% CI, 0.80–1.40). In the trial comparing spironolactone with tetracycline or ketoconazole, spironolactone did not show improvement in acne lesion count compared with tetracycline (n=140; RR 1.21; 95% CI, 0.92–1.60) or ketoconazole (n=140; RR 0.99; 95% CI, 0.90–1.08). This review also used 21 case series (N=728) and three clinical reports (N=2,290) to serve as supplementary efficacy data; when the pooled data from the case series was dichotomized, 77.6% (427/550 women) of the intention-to-treat population and 94.1% (10 trials, 427/454 women; risk ratio [RR] 1.22; 95% CI, 1.13–1.32) of the per-protocol population had any improvement of acne (measured as a physician-assessed 4- or 5-point Likert scale or recorded as improved/not improved) when using spironolactone at any dose. The most common side effect reported in both the case series and the RCTs was menstrual irregularities, 13.4% in the RCTs, and 33.4% in the case series or clinical reports. The incidence of menstrual irregularities appeared significantly lower when spironolactone was used concomitantly with a combined oral contraceptive (10 trials, N=258; RR 0.24; 95% CI, 0.11–0.56). All the studies included were deemed to have "high risk" of bias and had "low" or "very low quality" of evidence for all outcomes. Although the systematic review was not funded, only one trial affirmed that they did not receive financial support from a pharmaceutical company and only two trials provided declarations that stated no conflicts of interest; six trials did not disclose sources of funding though two received treatment medication from a spironolactone manufacturer, and one trial was funded by a company producing spironolactone.

A 2020 retrospective case series (n=395) evaluated the effectiveness and safety of spironolactone for acne for adult women.[2] Patients were women 21 to 66 years old, median age 32 years old. Acne was diagnosed by a dermatologist and included any severity including grade 1 (comedonal acne), grade 2 (mild-to-moderate papulopustular acne),

grade 3 (severe papulopustular/moderate nodular acne), and grade 4 (several nodular/conglobate acne). Treatment was oral spironolactone (average of 100 mg daily with a range of 25–200 mg daily) for a median treatment time of 13 months, with a range of 3 to 132 months. Treatment efficacy was assessed by the treating dermatologist using four categories: complete response (defined as >90% improvement), partial response (either >50% or ≤50% improvement), or no response. The mean time from initiation of treatment to maximum response was 5.7 months (range, 1–21 months). At study completion, 91.4% of all patients had some acne improvement with spironolactone, and 66.1% had complete response. All groups (acne grades 1–4) had a predominance of complete response, with 100% complete response in grade 1 (n=2), 63.7% complete response in grade 2 (n=100), 68.8% complete response in grade 3 (n=106), and 64.4% complete response in grade 4 (n=53). Twenty-five patients (6.3%) discontinued treatment because of adverse effects (dizziness, menstrual irregularity, fatigue, headaches, lightheadedness, and increase in urinary frequency). This study was limited by measuring response to treatment only at initial time of treatment and not at time of final dose, and inability to control for confounding factors including concomitant OCP use (in 113 patients). EBP

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References

1. Layton AM, Eady EA, Whitehouse H, et al. Oral spironolactone for acne vulgaris in adult females: a hybrid systematic review. *Am J Clin Dermatol.* 2017;18(2):169-191. [STEP 2]
2. Roberts E, Nowsheen S, Davis MD, et al. Treatment of acne with spironolactone: a retrospective review of 395 adult patients at Mayo Clinic, 2007-2017. *J Eur Acad Dermatol Venereol.* 2020;34(9):2106-2110. [STEP 4]

Does the supplemental use of *Ginkgo biloba* relieve symptoms in patients with dementia?

EVIDENCE-BASED ANSWER

Yes. *Ginkgo biloba* supplementation improves cognitive symptoms in elderly patients with mild to moderate dementia compared with placebo by about seven percent. However, it does not affect symptoms of dementia associated with psychosis such as euphoria or hallucinations (SOR: **A**, meta-analysis of randomized control trials). *Ginkgo biloba* may be as effective as donepezil in cognitive symptoms and may have fewer side effects (SOR: **B**, retrospective cohort).

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A 2018 meta-analysis of four randomized control trials (N=1,628) examined *Ginkgo biloba* supplementation on treating symptoms in elderly patients with dementia.[1] Patients were a mean age of 66 years old, 68% female, and all had mild to moderate dementia based on verified clinical instruments. Patients were randomized to either a specific *Ginkgo biloba* extract (designated Egb 761) of 240 mg or a similarly sized placebo pill. Outcomes were measured using a 12-item survey of symptoms for patients and the same survey for caregiver distress. Patient symptoms were scaled from 1 to 12 and caregiver distress was scaled 1 to 5, with higher scores indicating worsening severity. A clinician assigned scores for both the patients and the caregivers based on interviews with the caregiver. After pooling of all four trials, the *Ginkgo biloba* group experienced the largest improvements in apathy symptoms (mean difference [MD] –0.82; 95% CI, –1.0 to –0.64) and sleep/nighttime disturbance (MD –0.64; 95% CI, –0.80 to –0.47) compared with placebo. The only two items that saw no improvement with *Ginkgo biloba* supplementation were delusions and hallucinations. Because delusions and hallucinations were noted as being less common

symptoms in dementia, the authors noted that improvements in these areas would have been unlikely. Caregivers noted the most significant improvements in the dementia patients' agitation (MD –0.62; 95% CI, –0.8 to –0.44) and depression levels (MD –0.57; 95% CI, –0.69 to –0.44) for those treated with *Ginkgo biloba* compared with the placebo groups. Again, no improvement was noted in the caregivers' perception of the patients' delusions or hallucinations nor, additionally, their perception of the patients' euphoria.

A 2018 retrospective cohort analysis (n=189) evaluated the effectiveness of *Ginkgo biloba* extract EGb 761 compared with donepezil in elderly patients suffering from Alzheimer disease.[2] Patients were 80 years old or older and had an ICD-10 diagnosis of dementia with Alzheimer disease and an initial mini-mental state examination (MMSE) score of at least 10 points. Patients were either treated with ginkgo 761 (n=93) or 5 to 10 mg of donepezil (n=96). The primary outcome was improvement in MMSE scores, and results were controlled for by differences in age, gender, and instrumental activities of daily living. The 12-month posttreatment MMSE found no significant difference in cognitive decline between EGb 761 and donepezil (χ^2=1.54, *P*=.46). However, more adverse events were found in the donepezil group; these adverse events were not specified and simply stated as the reason a patient withdrew from the study. EBP

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References

1. Savaskan E, H Mueller, Hoerr R, von Gunten A, Gauthier S. Treatment effects of Ginkgo biloba extract EGb 761® on the spectrum of behavioral and psychological symptoms of dementia: meta-analysis of randomized controlled trials. *Int Psychogeriatrics*. 2018;30(3):285-293. [STEP 1]
2. Rapp M, Burkart M, Kohlmann T, Bohlken J. Similar treatment outcomes with Ginkgo biloba extract EGb 761 and donepezil in Alzheimer's dementia in very old age: a retrospective observational study. *Int J Clin Pharmacol Ther*. 2018; 56(3):130-133. [STEP 2]

In pregnant women with inherited thrombophilias, does prophylactic anticoagulation with low-molecular-weight heparin improve the chance of live birth rate?

EVIDENCE-BASED ANSWER

Low-molecular-weight heparin (LMWH) does not improve live birth rates in pregnant women with inherited thrombophilias (SOR: **B**, meta-analysis of randomized controlled trials with high heterogeneity). The American College of Obstetrics and Gynecology does not recommend LMWH to prevent adverse pregnancy outcomes in patients with inherited thrombophilias (SOR: **C**, expert consensus).

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A 2016 systematic review and meta-analysis of eight randomized controlled trials (RCTs; N=483) examined the effectiveness of low-molecular-weight heparin (LMWH) for pregnant women with an inherited thrombophilia to improve live birth rates.[1] Patients had a history of either recurrent early pregnancy loss, defined as two or more pregnancy losses before 10 weeks' gestation, or late pregnancy loss, defined as any pregnancy loss at 10 weeks' gestation or greater. Inherited thrombophilias were factor V Leiden, antithrombin deficiency, methylenetetrahydrofolate reductase gene mutation, prothrombin gene mutation, and protein C or protein S deficiency. The average gestational age at trial enrollment was between 5.2 and 11.9 weeks. The intervention groups received LMWH (enoxaparin 40 mg/d, dalteparin 5,000 IU/d, or nadroparin [not available in the United States] 2,850–3,800 IU/d) with or without aspirin (75–100 mg/d). The control groups received no treatment, aspirin

80 to 100 mg/d, or placebo. The review did not provide data on gestational age at the start of therapy or treatment duration. The primary outcome was live birth rate. In meta-analyses, the researchers calculated the relative risk (RR) of live births comparing LMWH with control interventions, where a RR <1 favored LMWH. Pooled analysis showed no difference in live birth rates between the LMWH and control groups (8 RCTs, N=483; RR 0.81; 95% CI, 0.55–1.2; I^2=91.9%). In subgroup analyses, LMWH was not superior to control interventions for improving live birth rates either among women with prior recurrent early pregnancy losses (5 RCTs, N=308; RR 0.81; 95% CI, 0.38–1.7; I^2=95.3%) or in those with a previous late pregnancy loss (3 RCTs, N=66; RR 0.97; 95% CI, 0.38–1.2; I^2 not given). Reported side effects of LMWH included skin reaction at injection site, bruising, itching, and nose bleeds; however, the systematic review did not pool adverse event data. Limitations included possible risk of bias because of unclear blinding of outcome assessors and small sample sizes (5 trials had fewer than 50 patients).

A 2018 expert consensus guideline from the American College of Obstetrics and Gynecology recommended against prophylactic anticoagulation for the prevention of adverse pregnancy outcomes (including fetal loss) in women with inherited thrombophilias, based on inconsistent findings in individual RCTs and lack of efficacy in meta-analyses[2] (recommendation level B, limited or inconsistent scientific evidence). EBP

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References

1. Skeith L, Carrier M, Kaaja R, et al. A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. *Blood* 2016;127(13): 1650-1655. [STEP 2]
2. Practice Bulletin No. 197 Summary: inherited thrombophilias in pregnancy. *Obstet Gynecol*. 2018;132(1): 249-251. [STEP 5]

Is a low serum 25-hydroxy vitamin D level (25OH-D) associated with worse disease severity in patients with rheumatoid arthritis?

EVIDENCE-BASED ANSWER

Vitamin D deficiency is common in patients with rheumatoid arthritis and is associated with increased disease severity (SOR: **A**, meta-analysis of observational studies, prospective cohort, and cross-sectional study).

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A 2016 systematic review and meta-analysis study of 24 articles (N=3,489) investigated the relationship between serum vitamin D (25-hydroxy vitamin D [25OH-D]) level and rheumatoid arthritis (RA) disease activity.[1] Reviewers included observational studies of adults with prediagnosed RA and data on serum 25OH-D. They calculated the pooled odds ratio (OR) for vitamin D deficiency (25OH-D <50 nmol/L) in patients with RA versus healthy controls. The correlation between 25OH-D levels and RA disease activity (ie, Disease Activity Score in 28 joints [DAS28], C-reactive protein [CRP], and erythrocyte sedimentation rate [ESR]) was calculated using correlation coefficients. No difference was observed between 25OH-D deficiency in patients with RA and healthy controls, and heterogeneity was high. However, in 12 studies, patients with RA had lower 25OH-D levels than healthy controls (mean difference of –16.52 nmol/L; 95% CI, –18.85 to –14.19 nmol/L). The reviewers found an inverse correlation between 25OH-D and both DAS28 (15 studies; r=–0.13; 95% CI, –0.16 to –0.09, $P<.001$) and CRP (5 studies; r=–0.12, 95% CI, –0.23 to –0.00, $P=.04$), which they concluded gave moderately strong evidence for a correlation between higher 25OH-D levels and decreased RA disease severity. No correlation was observed between 25OH-D and ESR.

A 2020 cohort study evaluated the association between baseline serum 25OH-D level and RA disease activity, disability, and radiologic damage over the first year of diagnosis in patients who met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria.[2] The study included 645 patients with ≥2 swollen joints for less than six weeks and less than six months, no disease-modifying antirheumatic drugs (DMARDs) or steroid treatments for ≥2 weeks, and DMARDs and steroids stopped two weeks before inclusion. The baseline serum 25OH-D level determined participant categories: deficiency, group 1 (25OH-D <10 ng/mL, n=114 [17.7%]); low level, group 2 (25OH-D=10–29.9 ng/mL, n=415 [64.5%]); and normal, group 3 (25OH-D ≥30 ng/mL, n=114 [17.7%]). At baseline and each visit, they assessed the DAS28 based on ESR (DAS28-ESR) with a score >5.1 considered severe disease and a Health Assessment Questionnaire Disability Index (HAQ-DI) with a score ≥0.5 considered relevant disability. They also collected the patient's global assessment on a 0 to 100 visual analog scale, ESR, CRP level, and quality of life evaluated by the Medical Outcomes Study Short Form–36. Radiographs of hands, wrists, and forefeet were taken at baseline and six and 12 months to assess radiographic progression as defined by an increase of at least one unit using the van der Heijde scoring system modified total sharp score (mTSSS) (on a scale of 0–440)[3]. DAS28-ESR at baseline was higher in group 1 than in combined groups 2 and 3 (5.65 vs 5.33, *P*=.007). A higher percentage of patients in group 1 had a DAS28-ESR score >5.1 (66% vs 56%), but the difference was not significant. However, there was an association of vitamin D deficiency with increased baseline ESR (OR 2.67, 95% CI, 1.76–4.05; *P*<.0001) and CRP levels (OR 1.64, 95% CI, 1.09–2.47; *P*=.018). The baseline HAQ-DI was higher in group 1 compared with the combined groups (1.24 vs 1.01, *P*=.001), at six months (0.75 vs 0.53, *P*=.002) and at 12 months (0.68 vs 0.51, *P*=.027). At six months, more patients in group 1 had a HAQ-DI score >0.5 than in groups 2 and 3 combined (61.2% vs 45.8%; OR 1.87, 95% CI, 1.20–2.91), but not at 12 months. At baseline, mean (SD) mTSS was higher but not significant in group 1 than in groups 2 and 3. However, the increase in mTSS in group 1 at six and 12 months was higher compared with the other groups (9.80 vs 6.99, *P*=.014 and 10.38 vs 7.73, *P*=.033, respectively). The study was limited by vitamin D supplementation by some patients at baseline, although they constituted a very small proportion of the study population.

A 2017 cross-sectional cohort study assessed whether vitamin D status in patients with RA correlates with disease activity, disability, and quality of life outcomes.[4] Patients 25 to 65 years old, diagnosed with RA (using ACR/EULAR criteria) for at least a year, on a stable DMARD regimen at least three months prior, and on ≤7.5 mg/day of prednisone or equivalent, for at least one month before enrollment were included in the study. Researchers measured serum 25OH-D levels in patients with RA (n=625) and healthy controls (n=276) and classified the results as normal (30 ng/mL), insufficient (20–30 ng/mL), or deficient (<20 ng/mL) levels. Thirty-six percent (n=223) of the RA group reported taking vitamin D 1000 IU/d for at least six months. The Rheumatoid Arthritis Impact Diseases score ([RAID], a scale of 0 to 10, with 0 indicating a low activity score and 10 indicating severe activity),[5] DAS28-CRP level, and HAQ-DI were evaluated on the day of blood sampling. The mean serum 25OH-D concentration in patients with RA was significantly lower compared with the control group (17.62 vs 18.95 ng/mL; *P*=.01). A negative correlation was observed between 25OH-D levels and measured outcomes DAS28-CRP, RAID, and HAQ-DI (*P*=.0001, *P*=.04, and *P*=.2, respectively). Vitamin D supplementation was associated with a higher DAS28-CRP score compared with nonsupplementation (3.4 vs 3.8, *P*=.009). EBP

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References

1. Lin J, Liu J, Davies ML, Chen W. Serum vitamin D level and rheumatoid arthritis disease activity: review and meta-analysis. *PLoS One*. 2016;11(1):e0146351. [STEP 1]
2. Mouterde G, Gamon E, Rincheval N, et al. Association between vitamin D deficiency and disease activity, disability, and radiographic progression in early rheumatoid arthritis: the ESPOIR cohort. *J Rheumatol*. 2020;47(11):1624-1628. [STEP 2]
3. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with

Concomitant Therapy Study Group. *N Engl J Med*. 2000; 343(22):1594-1602. [STEP 2]

4. Vojinovic J, Tincani A, Sulli A, et al. European multicentre pilot survey to assess vitamin D status in rheumatoid arthritis patients and early development of a new Patient Reported Outcome questionnaire (D-PRO). *Autoimmun Rev*. 2017;16(5):548-554. [STEP 2]
5. Mistry J, Sharif M, Prideaux A, et al. Use of rheumatoid arthritis impact of disease (RAID) in routine care; identification of DAS28 remission and unmet patient-reported outcomes. *Rheumatol Adv Pract*. 2020;4(2):rkaa013. [STEP 2]

Is chamomile effective to treat cyclic menstrual pain?

EVIDENCE-BASED ANSWER

Perhaps. Chamomile extract capsules taken before menses appear comparable with NSAIDs for reducing the overall severity of menstrual symptoms, with an equal effect on pain while improving psychological symptoms more (SOR: **B**, single randomized controlled trial [RCT]). Daily chamomile extract may also decrease cyclic mastalgia (SOR: **C**, small RCT).

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A 2014 double-blind randomized controlled trial (RCT; n=118) evaluated the effects of chamomile extract on premenstrual syndrome (PMS) symptoms among adult female students from a single university.[1] Patients were diagnosed with PMS after two consecutive menstrual periods and those with an abnormal body mass index (undefined), irregular cycles, or using other medications or supplements were excluded. The intervention group received 100 mg chamomile capsules three times a day for seven days, from 21st day of cycle until next onset of menses. The control group received 250 mg mefenamic acid capsules three times a day for seven days, from 21st day of cycle until next onset of menses. Patients filled out a daily 30-item PMS questionnaire on physical and psychological intensity of symptoms for at least two consecutive cycles and responses were converted to a percentage of severity 0% to 100%, with higher scores indicating higher severity. Loss to follow-up or exclusion because of improper use of medication was substantial, with 24% (14 patients in each group) lost to follow-up or excluded from analyses. After two months, those in the chamomile group had significantly greater improvement in overall severity scores over baseline compared with those in the mefenamic group (mean difference [MD] –29% vs –16%, $P=.04$). Also, psychological symptoms were significantly improved in the chamomile group compared with the mefenamic acid group (MD 33–11%, $P<.0001$). No difference was observed in improvement in other physical symptoms between the chamomile and mefenamic acid groups. The authors reported (no numerical evidence given) that side effects were more severe for menstrual bleeding in chamomile group and for gastrointestinal complications in the mefenamic acid group.

A 2018 double-blind RCT (n=60) assessed the effectiveness of chamomile on pain from cyclic mastalgia among adult women.[2] All patients reported a breast pain score of at least three on a 0 to 10 visual analogue scale (VAS) and were premenopausal with no serious medical illnesses. The chamomile group (n=30) added five drops of chamomile extract to water three times a day, and the placebo group (n=30) added five drops of distilled water to water three times a day, for two months. The measured outcome was pain measured on the 0 to 10 VAS and a daily breast pain chart (no scale given), collected in person or through telephone follow-ups every two weeks for two months. Both scales were combined into a single scale, which was not defined. After two months, those treated with chamomile observed a significantly greater reduction in baseline pain scores compared with the placebo group (MD –15 vs –6, $P=.004$). As per protocol analysis, five patients were excluded because of loss to follow-up or self-discontinuation of treatment. No significant side effects were reported in either group. Limitations included lack of information on the final outcome scale and no defined concentration of chamomile extract used. EBP

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References

1. Sharifi F, Simbar M, Mojab F, Majd HA. Comparison of the effects of Matricaria chamomila (Chamomile) extract and mefenamic acid on the intensity of premenstrual syndrome. *Complement Therapies Clin Pract.* 2014;20(1):81-88. [STEP 2]
2. Saghafi N, Rhkhshandeh H, Pourmoghadam N, et al. Effectiveness of Matricaria chamomilla (chamomile) extract on pain control of cyclic mastalgia: a double-blind randomised controlled trial. *J Obstet Gynaecol.* 2018;38(1):81-84. [STEP 2]

Does PSA screening decrease overall mortality in men over 45 years old?

EVIDENCE-BASED ANSWER

No, prostate-specific antigen screening for average-risk men between 50 and 74 years old does not decrease all-cause mortality compared with usual practice (SOR: **A**, 5 meta-analyses and 1 extended outcome report).

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A 2015 systematic review of four meta-analyses analyzed potential mortality reduction with prostate-specific antigen (PSA)-based screening.[1] Included patients were asymptomatic men, in North American and Western Europe, 50 to 80 years old (although majority of trials did not include men 75–80 years old). Researchers excluded patients with a previous diagnosis of prostate cancer or recent PSA screening. In all studies, the intervention was PSA screening every 1 to 4 years, often accompanied by a digital rectal examination (DRE) for the first few years. If PSA screening or DRE was abnormal, diagnostic evaluation through biopsy was pursued. Control groups were not screened by PSA or DRE through the study, although one trial allowed for usual medical practice that could include PSA screening. The primary outcome was all-cause mortality, with follow-up intervals ranging from 4 to 20 years. Four meta-analyses directly addressed the primary outcome. In all four meta-analyses, PSA-based screening did not decrease all-cause mortality (n=341,342, relative risk [RR] 1.0, 95% CI, 0.96–1.0; n=256.019, RR 0.99, 95% CI, 0.97–1.0; n=266,750, RR 0.99, 95% CI, 0.98–1.0; n=206,393, RR 0.90, 95% CI, 0.75–1.1). Limitations included heterogeneity in primary treatment for prostate cancers, PSA thresholds for biopsy, screening frequency, and intervals.

A 2018 meta-analysis (5 RCTs, N=721,718) investigated the effect of PSA-based screening on all-cause mortality.[2] The systematic review included one new RCT as well as extended follow-up data from four RCTs. Patients included asymptomatic men, 50 to 74 years old, from the U.S., Canada, and Europe. Exclusion criteria were previous prostate cancer diagnoses and recent PSA screening. Patients in the intervention arm were offered PSA screening every 1 to 4 years with diagnostic biopsy performed for positive screens. Patients in the control arm were not screened, although one study allowed for usual medical practice that could include PSA screening. The primary outcome was all-cause mortality measured at 10 to 20 years of follow-up. No difference in all-cause mortality was observed between the PSA screening group and the control group (incident rate ratio 0.99; 95% CI, 0.98–1.0). Limitations included heterogeneity in primary treatment, thresholds for biopsy, and screening frequency and interval. In addition, PSA screening in the control arm may have reduced the effects of the intervention.

A 2016 extended outcome report from a multicenter RCT (n=76,685) studied all-cause mortality with PSA-based screening versus control.[3] Included patients were asymptomatic men between 55 and 74 years old. Exclusion criteria were history of prostate, lung, and colon cancer, current cancer treatment, or more than one previous PSA test in the past three years. The intervention group received PSA and DRE screening at baseline and then PSA screening annually for five years and DRE screening annually for three years. Those in the control group were offered no screening but some received PSA screening in the community. The primary outcome was all-cause mortality at up to 19 years of follow-up (median 15 years). PSA-based screening did not reduce all-cause mortality compared with the control group (RR 0.98; 95% CI, 0.95–1.0). These extended outcomes were not referenced in the previous systematic reviews, although the original RCT and previous extended outcome report were. EBP

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References

1. Pron G. Prostate-specific antigen (PSA)-based population screening for prostate cancer: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2015;15(10):1-64. [STEP 1]
2. Ilic D, Djulbegovic M, Jung JH, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. *BMJ*. 2018;362:k3519. [STEP 1]
3. Pinsky PF, Prorok PC, Yu K, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. *Cancer*. 2017;123(4):592-599. [STEP 2]

Is hydrotherapy an effective treatment of fibromyalgia?

EVIDENCE-BASED ANSWER

Yes, various forms of hydrotherapy (excluding exercises in city or tap water) taken together produce moderate improvements in pain and moderate-to-large improvements in quality of life in patients with fibromyalgia (SOR: **B**, 2 meta-analyses of low-quality randomized controlled trials).

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A 2014 meta-analysis of 22 randomized controlled trials (RCTs; N=639) assessed the effectiveness of hydrotherapy in the management of fibromyalgia.[1] This paper included two different types: hydrotherapy, any treatments using tap water (most of the RCTs involved exercises in water and not pertinent to this review), and balneotherapy, any treatments using any other substances such as thermal or mineral water. All patients who received balneotherapy had fibromyalgia as diagnosed according to the 2010 American College of Rheumatology criteria with a median disease duration of 8.4 years. The age of patients ranged from 18 to 73 years old (median 45–46 years old) and were predominantly (96%) female. Five of the balneotherapy intervention groups received sulfur baths (2 trials) or baths in mineral/thermal water (3 trials), with a treatment duration of 1.5–12.0 weeks (median, 2.0 weeks) and follow-up at 3.5 months. Minutes spent in immersion was not reported. Control groups received no treatment or any other active therapy (examples were not given). Pain was assessed using several different versions of a 10-point visual analog scale (VAS), and quality of life was assessed using the 100-point health-related quality of life (HRQOL) measure. Balneotherapy demonstrated a moderate decrease in pain on VAS (5 trials; N=177; standardized mean difference [SMD] –0.84; 95% CI, –1.36 to –0.31; I^2=63%) and HRQOL (4 trials; N=137; SMD –0.78, 95% CI, –1.13 to –0.43; I^2=0%). At follow-up, the improvement was maintained for both pain (SMD –0.25; 95% CI, –0.50 to –0.01; I^2=0%) and HRQOL (SMD –0.35; 95% CI, –0.61 to –0.10; I^2=0%). Unspecified minor adverse effects were only reported in four trials. This paper was limited by the lack of blinding in some trials, small sample sizes, and risk of bias.

A 2009 meta-analysis of 10 RCTs (N=446) evaluated the effectiveness of hydrotherapy in fibromyalgia.[2] Four of these RCTs were also included in the meta-analysis as above. Patients were between 18 and 65 years old (mean age, 46 years old) and predominantly (95%) female. Although patients with diagnosis of fibromyalgia based on unspecified "recognized criteria" were included, patients with inflammatory arthritic diseases were excluded. The interventions included whirl baths (1 trial), thermal baths (4 trials), sulfur pool (1 trial), Stanger bath (type of galvanic bath; 1 trial), mud bath followed by thermal water (1 trial), hydro galvanic bath (type not specified; 1 trial), and mud bath with hot air (1 trial). None of the interventions involved exercises in city or tap water. Treatment duration was 20 to 25 minutes. Patients received 3 to 6 treatments per week across the trials. Treatment duration was two weeks for four trials, three weeks for two trials, "3 to 4 weeks" for one trial, and five weeks for one trial, and two trials quantified the treatment course as 10 treatments in total rather than a certain number of weeks. The control groups received any other intervention (eg, unspecified "therapy as usual," relaxation exercises, or whirl baths with plain water) or no intervention. Outcomes were pain as assessed through a standard 10-point VAS, with higher numbers indicating more pain, and quality of life as assessed using

the 100-point HRQOL measure, where a higher number indicates higher disease burden. Overall, these hydrotherapies produced a moderate reduction of pain on the VAS (9 trials; N=318, SMD –0.78; 95% CI, –1.42 to –0.13; I^2=83%) and largely improved quality of life on the HRQOL (4 trials; SMD=–1.67; 95% CI, –2.91 to –0.43; I^2=90%). These effects were sustained at follow-up (follow-up was at 6–36 weeks, median 14), with a large pain reduction persisting on the VAS (4 trials; N=160, SMD –1.27; 95% CI, –2.15 to –0.38; I^2=84%) and a large improvement in quality of life persisting on the HRQOL (4 trials; N=202, SMD –1.16; 95% CI, –1.96 to –0.36; I^2=84%). Subgroup analysis for pain improvement indicated statistical significance only in the RCTs involving bathing in thermal or mineral water (5 trials; N=184; $P<.0001$; SMD –1.63; 95% CI, –.231 to –0.96; I^2=73%), whereas trials with whirl baths, mud baths, and Stanger bath did not (3 trials; N=134, SMD 0.01; 95% CI, –0.45 to 0.47; I^2=12). Only one RCT reported side effects, with a 10% incidence of slight "flushing." This paper was limited by the absence of intention-to-treat analysis or adequate blinding in any studies, by only three RCTs having sample sizes of at least 25 per group, and by the method of randomization generally not being reported.

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

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References

1. Naumann J, Sadaghiani C. Therapeutic benefit of balneotherapy and hydrotherapy in the management of fibromyalgia syndrome: a qualitative systematic review and meta-analysis of randomized controlled trials. *Arthritis Res Ther.* 2014;16(4):R141. [STEP 1]
2. Langhorst J, Musial F, Klose P, et al. Efficacy of hydrotherapy in fibromyalgia syndrome—a meta-analysis of randomized controlled clinical trials. *Rheumatology (Oxford)* 2009;48:1155-1159. [STEP 1]

Does the use of albumin in adults with septic shock in the ICU decrease mortality?

EVIDENCE-BASED ANSWER

In intensive care unit patients with septic shock, albumin infusion does not improve mortality compared with crystalloids (SOR: **A**, systematic review and meta-analysis of randomized controlled trials [RCTs]). Similarly, no benefit to add albumin to lactated Ringer's solution is noted in cancer patients with severe sepsis or septic shock (SOR: **B**, single RCT).

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A 2018 meta-analysis of six randomized controlled trials (RCTs; N=3,088) compared the effects of albumin and crystalloid on mortality in patients with septic shock.[1] With the exception of one paper published in 1983, all other papers included patients with septic shock managed within the intensive care unit (ICU) setting. Patients' median or mean ages were between 58 and 79 years old, with 35% to 44% females, and drawn from 10 countries of America, Europe, and Oceania from 1983 to 2015. Patients were diagnosed with septic shock based on an identified infection focus and presence of ≥2 (out of 4) systemic inflammatory response syndrome criteria. For the albumin group, patients were given 20% albumin (2 trials), 4% or 5% albumin (3 trials), and both concentrations (1 trial). For the crystalloid group, patients were given normal saline (4 trials), lactated Ringer's (LR) solution (1 trial), and different kinds of crystalloid products (1 trial). The primary outcome was all-cause death at 28 or 30 days, whereas the principal secondary outcome was 90-day mortality. No significant improvement was found regarding all-cause mortality in the albumin group compared with the crystalloid solutions group (6 trials, N=3,088; risk ratio [RR] 0.91; 95% CI, 0.83–1.00; I^2=0%). Use of albumin did not decrease 28-day mortality (6 trials, N=3,088; RR 0.96; 95% CI,

0.83–1.11; I^2=1%) or 90-day mortality (6 trials, N=3,088; RR 0.89; 95% CI, 0.79–1.00; I^2=0%). Limitations of the study included nonblinded method and different follow-up durations.

A 2019 single-center RCT (n=360) compared the effects of LR solution and 4% albumin in LR in the early resuscitation phase in sepsis.[2] Patients ranged in age from 51 to 70 years old, and 53% of the albumin group and 50% of the crystalloid group were males. All patients had a cancer diagnosis and were admitted to the ICU because of severe sepsis or septic shock within the previous six hours. Half of the patients received a bolus of 4% albumin in 500 mL LR solution, and the other half received 500 mL LR solution only. The primary outcome was all-cause mortality at seven days. Secondary outcomes were all-cause mortality within 28 days among other outcomes. At seven days, no significant difference was observed in death between the two groups (26% in the albumin group vs 22% in the LR group; odds ratio [OR] 1.2; 95% CI, 0.74–1.95). No significant difference was also observed in mortality at 28 days (53% in the albumin group vs 46% in the LR group; OR 1.34; 95% CI, 0.88–2.02). No significant differences in the other secondary outcome were observed. Limited generalizability of findings to cancer patients was a key limitation of the study. EBP

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References

1. Zou Y, Ma K, Xiong JB, et al. Comparison of the effects of albumin and crystalloid on mortality among patients with septic shock: systematic review with meta-analysis and trial sequential analysis. *Sao Paulo Med J.* 2018;136(5):421-432. [STEP 1]
2. Park CH, de Almeida JP, de Oliveira GQ, et al. Lactated Ringer's versus 4% albumin on lactated Ringer's in early sepsis therapy in cancer patients: a pilot single-center randomized trial. *Crit Care Med.* 2019;47(10):e798-e805. [STEP 2]

Is breastfeeding effective in reducing procedure-related pain in infants?

EVIDENCE-BASED ANSWER

Breastfeeding reduces crying time and heart rate in neonates undergoing heel lance or venipuncture and reduces validated pain scores as compared with placebo, positioning in mother's arms, and pacifier use (SOR: **A**, meta-analysis of randomized controlled trials [RCTs] and quasi-RCTs). Breastfed infants 1 to 12 months old undergoing vaccinations cry for less time and score lower on standardized pain scores than infants using a variety of other pain-reducing interventions (SOR: **A**, meta-analysis of RCTs and quasi-RCTs). The Academy of Breastfeeding Medicine recommends direct breastfeeding be continued throughout a procedure as the best means for control of procedure-related pain in infants (SOR: **C**, consensus guideline).

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A 2012 meta-analysis of randomized controlled trials (RCTs) and quasi-RCTs (20 studies, N=2,071) examined the effectiveness of breastfeeding or breast milk on reducing neonatal pain indicators resulting from blood sampling by venipuncture or heel lance.[1] Included patients were healthy term (≥37 weeks' gestation) and preterm (<37 weeks' gestation) neonates <2 months old. Investigators assigned patients in the intervention groups to receive breast milk directly from mother (10 studies, N=1,075) or through oral supplement (10 studies, N=996) during venipuncture or heel lance procedures. Patients more than two months old were excluded, as were trials that were not RCTs. Control group patients received a variety of other comforting interventions (water, glucose/sucrose, pacifier, holding, swaddling, lying on examination table, rocking, massage, or verbal comfort). Pain was assessed by measuring changes in vital signs (heart rate, oxygen saturation, and blood pressure), cry

variables (percent of time crying, duration in seconds, and duration of first cry in seconds), or validated pain scores. Pain scores used included the Premature Infant Pain Profile, Neonatal Infant Pain Scale (NIPS), Neonatal Facial Coding System (NFCS), and the nonvalidated Doleur Aigue Nouveau-ne. Pooling of results showed that direct breastfeeding reduced infant heart rate when compared with the infant being held by mother and given a pacifier (2 trials, N=126; mean reduction of 12 bpm; 95% CI, –19 to –5.1). Direct breastfeeding also reduced duration of crying when compared with no treatment (3 trials, N=179; mean reduction of 41 seconds; 95% CI, –50 to –33) and sucrose/glucose administration (3 trials, N=183; mean reduction of 5.8 seconds; 95% CI, –12 to –0.15). Breastfeeding reduced pain compared with placebo, positioning in mother's arms, and pacifier use as measured through validated neonatal pain scores (see **TABLE**). Breastfeeding did not consistently reduce pain scores compared with no intervention and oral sugar solutions. Supplemented expressed breast milk did not demonstrate consistent reduction in pain compared with control groups. This meta-analysis was limited by a lack of statistical analysis comparing pooled breastfeeding data to the pooled effect of all other control groups. Many of the RCTs were limited by inability to mask the intervention (breastfeeding).

A 2016 meta-analysis of RCTs and quasi-RCTs (10 studies, N=1,066) examined the effectiveness of breastfeeding on reducing infant pain while undergoing routine vaccination.[2] The studies included infants 28 days through 12 months old who presented for routine intramuscular or subcutaneous vaccinations. Infants <28 days old were excluded. The authors did not report composite demographic data regarding the average age of infants; however, only two of 10 studies included infants more than six months old. The intervention infants were breastfed before vaccination administration, and breastfeeding continued until the vaccination procedure was complete. The control group infants received no pain treatment or a variety of other pain-reducing interventions (oral dextrose, EMLA cream, massage therapy, or topical vapocoolant spray). The primary outcomes measured were cry duration and validated pain scores. Pain score systems included NIPS, NFCS, Modified Facial Coding System, Modified Behavioral Pain Scale, and the Wong-Baker FACES Pain Rating Scale. When compared with the pooled control group data, breastfed infants had a reduced mean difference in cry time of 38 seconds (6 trials, N=547; 95% CI, –50 to –26). Similarly, when pain scores were pooled and standardized on a scale of 0 to 10 (with 10 representing maximum pain), breastfed infants had a reduction in pain score of 1.7 (5 trials, N=310; 95% CI, –2.2 to –1.3) when compared with control groups. No harms were reported by any of the studies. This systematic review was limited by the lack of blinding of participants and high risk of bias for blinding outcome assessment.

An Academy of Breastfeeding Medicine Clinical Protocol published in 2016 provided recommendations for management of procedural pain in breastfed infants.[3] This evidence-based guideline recommended direct breastfeeding as the preferred approach for reducing pain from a procedure (quality of evidence IA, evidence from meta-analysis of RCTs). The guideline also noted that breastfeeding should not be stopped before the painful procedure (quality of evidence IB, evidence from at least one RCT). EBP

TABLE. Systematic review of randomized controlled trials evaluating breastfeeding for reduction of pain in neonates undergoing heel stick or venipuncture[1]

Comparison	Pain scale	No. of studies	No. of patients	Mean difference (95% CI)
Placebo	PIPP[a]	1	89	–6.0 (–7.4 to –4.5)
	DAN[b]	1	89	–6.0 (–7.4 to –5.1)
Positioning in mother's arms	PIPP	1	89	–7.5 (–9.0 to –6.0)
	NFCS[c]	2	120	–0.3 (–0.4 to –0.2)
	DAN	1	89	–6.8 (–7.8 to –5.8)
Pacifier	NFCS	1	61	–2.0 (–3.2 to –0.9)

[a] PIPP=Premature Infant Pain Profile (score range 0–21). [b] DAN=Douleur Aigue Nouveau-ne (score range 0–10). [c] NFCS=Neonatal Facial Coding System (score range 0–10).

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References

1. Shah PS, Herbozo C, Aliwalas LL, Shah VS. Breastfeeding or breast milk for procedural pain in neonates. *Cochrane Database Syst Rev.* 2012;(12):CD004950. [STEP 1]
2. Harrison D, Reszel J, Bueno M, et al. Breastfeeding for procedural pain in infants beyond the neonatal period. *Cochrane Database Syst Rev.* 2016;(16):CD011248. [STEP 1]
3. Reece-Stremtan S, Gray L, the Academy of Breastfeeding Medicine. ABM Clinical Protocol #23: Nonpharmacological management of procedure-related pain in the breastfeeding infant. *Breastfeed Med.* 2016;11:425-429. [STEP 4]

Does augmenting antidepressant medication in euthyroid patients with thyroid hormone supplement improve depression treatment?

EVIDENCE-BASED ANSWER

Supplementation of specific serotonin reuptake inhibitors with triiodothyronine (T3) does not improve depression treatment in euthyroid patients (SOR: **A**, meta-analysis, systematic review, and single randomized controlled trial [RCT]). Augmenting tricyclic antidepressants with T3 in euthyroid patients may accelerate the depression response rate during the early initiation period but is equivalent to placebo at four weeks (SOR: **B**, single RCT).

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A 2008 systematic review of five randomized controlled trials (RCTs) and three small open-label studies investigated whether T3 supplementation improved depression symptoms in euthyroid adult patients with major depressive disorder (MDD) treated with specific serotonin reuptake inhibitors (SSRIs).[1] The mean age of patients was approximately 40 years old, with a slight majority of patients being female. Methodological differences between studies prevented meta-analysis. Three enhancement studies initiated T3 and the SSRI concurrently, whereas two augmentation studies started T3 in patients who did not initially respond to SSRIs or lithium. The studies used different validated self-reporting depression rating scales that graded depression severity, with higher scores indicating worse depression. Rating scales included the Hamilton Depression Rating Scale (HAMD17 and HAMD21, range 0–52), Quick Inventory of Depressive Symptoms–Self-Report (range 0–42), and Montgomery–Asberg Depression Rating Scale (MADRS, range 0–60). The primary outcome in all studies was >50% reduction in the depression rating score. Two RCT augmentation studies (n=142 and 36) showed no difference in depression severity scores comparing SSRI plus T3 with SSRI plus placebo. The three enhancement RCTs demonstrated inconsistent results. Two studies (n=113 and 57) demonstrated no difference between placebo and T3 groups; the third study (n=124) found an improved response rate (T3: 69% vs placebo: 50%, number needed to treat [NNT]=11, P=.02) and a decreased remission rate with T3 supplementation (T3: 59% vs placebo: 38%, NNT=5, P=.02). The open-label studies were small (n=25, 19, and 11, respectively) and demonstrated no differences between treatment and control groups. Significant limitations of this systematic review included study variability in number of patients, type of SSRI, and length of treatment.

A 2009 meta-analysis (n=444) evaluated the effect of T3 in addition to antidepressants on depressive symptoms in euthyroid patients with acute nonpsychotic MDD of any severity.[2] All trials compared the use of an antidepressant at any dose and 25 to 50 μg T3 daily against antidepressants at equivalent doses with placebo. Inclusion criteria for these studies were nonpsychotic major depression in acute phase of treatment. In three trials, only SSRIs were used as antidepressants. In the fourth, 52% of patients were given SSRIs, and others given venlafaxine, bupropion, nefazodone, or mirtazapine. Two of the RCTs used in this meta-analysis were part of the 2008 systematic review, but this meta-analysis specifically reviewed patients without resistant MDD. All trials used the HAMD17 or the MADRS. Response was defined as 50% or greater reduction in either

HAMD17 or MADRS scores. Remission was defined as response criteria lasting at least six weeks. No difference was observed in response or remission rates at the endpoint. Limitations of this study included variability in dosing of SSRIs and inability to draw conclusions about other antidepressant classes.

A 2012, eight-week, double-blind RCT (n=153) studied the effects of augmentation of sertraline with T3 on depressive symptoms in euthyroid adults (18–60 years old) with nonpsychotic MDD.[3] Patients' mean age was 42 years old, 62% were female, and 79% were White. Those with any other Diagnostic and Statistical Manual of Mental Disorders, Edition IV psychiatric disorder in the past year, who were pregnant or breast-feeding, or with an unstable medical condition were excluded. Both treatment and placebo groups received initial dosing of sertraline 50 mg daily, increased by 50 mg as tolerated for therapeutic effect (maximum 200 mg), along with placebo or 25 μg per day of T3 for one week, increased to 50 μg per day for the treatment group in week 2. The primary outcome (termed response by the authors) was defined as 50% reduction in baseline HAMD21 and a total <15. The secondary outcome was remission (HAMD21 <8). Neither depression response nor remission rates decreased in patients augmented with T3 compared with placebo. Similar rates of adverse events were observed between placebo and T3 groups. Limitations of this study included a single-site protocol and a patient population that was not treatment-resistant or chronically ill.

A 2001 meta-analysis including six double-blind, randomized, placebo-controlled trials investigated 125 adult patients with nonrefractory MDD treated with tricyclic antidepressants (TCAs; imipramine or amitriptyline 100–200 mg) augmented with T3 (20–62.5 mg) or placebo for 21 to 28 days.[4] Patients were majority female and euthyroid. The primary outcome was improvement of HAMD17 by >50% or to less than eight. In five of six double-blind RCTs, patients met the primary outcome more quickly when T3 was administered with TCA in patients with MDD (pooled weighted effect size 0.58, 95% CI, 0.21–0.94; $P<.002$). An accelerated response occurred as early as two days post-treatment. After 28 days, no difference was observed in MDD primary outcome measures between treatment groups. Recent trials have not investigated TCA alone; therefore, further evidence to support this claim is unavailable. Study limitations included small patient population, varying doses and type of TCA, and varying doses of T3. EBP

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References

1. Cooper-Kazaz R, Lerer B. Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors. *Int J Neuropsychoph*. 2008;11(5):685-699. [STEP 1]
2. Papakostas GI, Cooper-Kazaz R, Appelhof BC, et al. Simultaneous initiation (coinitiation) of pharmacotherapy with triiodothyronine and a selective serotonin reuptake inhibitor for major depressive disorder: a quantitative synthesis of double-blind studies. *Int Clin Psychopharmacol*. 2009;24(1):19-25. [STEP 1]
3. Garlow SJ, Dunlop BW, Ninan PT, Nemeroff CB. The combination of triiodothyronine (T3) and sertraline is not superior to sertraline monotherapy in the treatment of major depressive disorder. *J Psychiatr Res*. 2012;46(11):1406-1413. [STEP 2]
4. Altshuler LL, Bauer M, Frye MA, et al. Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *Am J Psychiatry.* 2001;158(10):1617-1622. [STEP 1]

Are PCSK9 inhibitors alternatives for the treatment of hyperlipidemia in high-risk patients who are statin intolerant?

EVIDENCE-BASED ANSWER

Proprotein convertase subtilisin/krexin type 9 inhibitors have been shown superior to ezetimibe and placebo in lowering mean LDL cholesterol in statin intolerant patients who are at high risk of cardiovascular disease (SOR: **B**, meta-analysis of randomized controlled trials [RCTs] with low-quality and single RCT). Alirocumab given at 75 mg every two weeks has been shown to be more effective than alirocumab 150 mg given every four weeks in reducing LDL-C from baseline (SOR: **B**, single RCT).

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A 2021 meta-analysis of eight randomized controlled trials (RCTs) aimed to compare the reduction in LDL cholesterol (LDL-C) between proprotein convertase subtilisin/krexin type 9 (PCSK9) inhibitors and ezetimibe in patients not receiving statins (n=1,602).[1] Patients were an average of 58 years old, with 32–55.6% male. All trials were performed on adults not receiving statins or determined to have statin intolerance as identified by a statin rechallenge arm. The trials included PCSK9 inhibitors evolocumab (140 mg every 2 weeks or 420 mg every 4 weeks) and alirocumab (75 mg every 2 weeks or increased to 150 mg every 2 weeks depending on response). Overall, PCSK9 inhibitors were significantly more likely to reduce LDL-C levels than ezetimibe (8 trials, N=1,602; mean difference [MD] –36.5 mg/dL; 95% CI, –38.3 to –34.7; I^2=4%). A subgroup analysis of patients intolerant to statins also showed PCSK9 inhibitors were significantly more likely to reduce LDL-C than ezetimibe (5 trials, N=902; MD –36.1 mg/dL; 95% CI, –39.2 to –33.1; I^2=21%). Limitations included inconsistent endpoints for measuring LDL-C in each trial and varying definitions of statin intolerance.

A 2015 RCT, included in the analysis above, compared the LDL-C lowering effects and muscular symptoms of ezetimibe versus a PCSK9 inhibitor (alirocumab) in patients with statin intolerance and moderate to very high risk of cardiovascular disease (n=361).[2] Patients were an average of 63.4 years old, with 93.9% Caucasian, and 54.8% male. Statin intolerance was defined as failing at least two statins because of muscle symptoms. Patients at moderate or high risk for cardiovascular disease (defined using the systematic coronary risk evaluation score) were eligible if serum LDL-C was >100 mg/dL. Those at very high risk were eligible if LDL-C was >70 mg/dL. During a run-in period, patients received subcutaneous and oral placebo treatment for four weeks, and those who reported new-onset muscle-related symptoms were excluded. Patients were then randomized to double-blind alirocumab 75 mg every two weeks (Q2W) (n=126), ezetimibe 10 mg daily (n=125), or atorvastatin 10 mg daily (n=63). All patients received an oral or subcutaneous placebo to mask drug identification. LDL-C was measured at baseline and at eight, 12, and 24 weeks. Alirocumab was increased to 150 mg Q2W at week 12 based on LDL-C values at week 8. After 24 weeks, alirocumab reduced the baseline mean LDL-C by –45.0%, whereas ezetimbe reduced the mean LDL-C by –14.6% (MD –30.4%, P<.0001). More patients on alirocumab than patients on ezetimibe reached a goal LDL-C of <70 or <100 mg/dL, as determined by cardiovascular risk (42% vs 4.4%; P <.0001). Significantly fewer skeletal muscle-related events were observed with alirocumab than with atorvastatin (hazard ratio [HR] 0.61; 95% CI, 0.38–0.99). The rate of drug discontinuation after muscle-related adverse events was nonsignificant when comparing alirocumab with atorvastatin (HR 0.67; 95% CI, 0.34–1.32) and alirocumab to ezetimibe (HR 0.78; 95% CI, 0.43–1.41).

A 2016 phase 3, double-blind, placebo-controlled trial (n=233) compared the lipid-lowering effects of alirocumab 75 mg Q2W (n=116) and alirocumab 150 mg every four weeks (Q4W; n=59) versus placebo (n=58).[3] The majority of patients were statin intolerant (n=210), defined as failing at least two statins because of muscle symptoms. LDL-C was assessed at baseline and at eight and 24 weeks. Both alirocumab treatment arms of the study included possible dose increases to 150 mg Q2W at week 12 if LDL-C levels did not decrease to <70 mg/

dL for very high-risk participants, <100 mg/dL for moderate- to high-risk participants, or who did not achieve an overall reduction of LDL-C by 30% at week 8. The alirocumab 150 mg Q4W group experienced a reduction of LDL-C by 51.7% compared with 53.5% in the 75 mg Q2W group ($P < .0001$). Both the 150 mg Q4W and the 75 mg Q2W groups had a significant difference in the percentage of patients achieving their goal LDL-C when compared with placebo at 24 weeks (63.9% vs 70.3% vs 1.8%; $P < .0001$). The most common adverse event reported was injection site reactions, found to be more prevalent in the alirocumab 150 mg Q4W group than the 75 mg Q2W group (13.8% vs 3.5%, no *P* value reported). EBP

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References

1. Benhuri B, Ueyama H, Takagi H, et al. PCSK9 Inhibitors and ezetimibe monotherapy in patients not receiving statins: a meta-analysis of randomized trials. *Curr Vasc Pharmacol*. 2021;19(4):390–397. [STEP 1]
2. Moriarty P, Thompson P, Cannon C, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol.* 2015;9(6):758–769. [STEP 2]
3. Stroes E, Guyton JR, Lepor N, et al. Efficacy and safety of alirocumab 150 mg every 4 Weeks in patients with hypercholesterolemia not on statin therapy: the ODYSSEY CHOICE II study. *J Am Heart Assoc*. 2016;5(9):e003421. [STEP 2]