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EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

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EVIDENCE-BASED PRACTICE
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FPIN
Family Physicians Inquiries Network

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

TABLE OF CONTENTS

VOL 24 | NO. 9 | September 2021

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

IN DEPTH

DIVING FOR PURLs

GEMS

EBM ON THE WARDS

HELPDESK ANSWERS

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TABLE OF CONTENTS *Continued*

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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Are progesterone-only contraceptives safe in women with tobacco use or venous thromboembolic disease?

EVIDENCE-BASED ANSWER

Probably. Noninjectable progesterone-only contraceptives (POCs) do not increase the risk of recurrent venous thromboembolism (VTE) in women with tobacco use or a history of VTE (SOR: **B**, systematic review of cohort and case-control studies). Benefits outweigh the risks of POCs (SOR: **C**, two consensus guidelines), but women with an acute VTE should not use POCs (SOR: **C**, consensus guideline).

DOI 10.1097/EBP.0000000000001155

A 2016 systematic review of seven cohort and 13 case-control studies with over 19,000 patients assessed the risk of venous thromboembolism (VTE), stroke, and acute myocardial infarction among women using progesterone-only contraceptives (POCs) who had risk factors of smoking or history of previous VTE.[1] Included women had conditions that increased their risk of VTE, such as a prior history of VTE, thrombogenic mutations, postpartum state, sickle cell disease, systemic lupus erythematosus, smoking, diabetes, and hypertension. Women from the general population without elevated risk of VTE were also included. Patients with acute VTE were excluded. Women were of child-bearing age, and follow-up ranged from two years to 22 years. Analysis did not demonstrate increased odds of VTE with progesterone-only pills, implants or progesterone-containing intrauterine devices. No significant increased occurrence of VTE was noted in smokers using progesterone-only pills compared with nonusers and nonsmokers in either the first (n=11,134, odds ratio [OR] 2.4; 95% CI, 0.7–8.3) or the second (n=2,760, OR 0.95; 95% CI, 0.2–6.0) large case-control studies. One cohort study (n=92) examined women with a history of VTE who used POCs and found no elevated risk of recurrent VTE compared with those who did not use hormones (OR 3.6; 95% CI, 0.7–17.3). Two small cohort studies examined use of noninjectable POCs (pills, progesterone-containing intrauterine devices and implants) in women with a prior VTE, and neither study found elevated odds of recurrent VTE compared with those who did not use hormones. One case-control study (n=1,850) found an increased risk of VTE with injectable POCs in women with the Factor V Leiden mutation compared with those without the mutation (OR 17.0; 95% CI, 2.4–714). Another case-control study (n=13,694) did not find an increased risk from injectable POCs in smokers compared with the control group. Occurrences of acute myocardial infarction and stroke were not elevated among smokers using progesterone-only pills compared with nonusers.

The 2016 Centers for Disease Control and Prevention (CDC) US Medical Eligibility for Contraceptive Use evidence-based guideline stated that the benefits likely outweigh the risks of POCs regardless of potential increased risk for VTE (no strength of recommendation given).[2] The CDC also stated that the benefit also likely outweighs the risks for injectable POCs in women with multiple cardiovascular risks, including smoking (no strength given).

The World Health Organization's (WHO) 2015 Medical Eligibility Criteria for Contraceptive Use recommended that there should be no restriction on the use of noninjectable POCs for cigarette users.[3] The WHO also stated that for patients with a history of VTE, whether anticoagulated or not, as well as for patients with a known thrombogenic mutation, the advantages of using noninjectable POCs generally outweighed the risks. The guideline stated that for patients with acute VTE using injectable POCs, the risks usually outweigh the advantages, and for patients using injectable POCs who have multiple cardiovascular risk factors, including smoking, the risks may outweigh the benefits (no strength given). EBP

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3. World Health Organization. *Medical Eligibility Criteria for Contraceptive Use*. 5th ed; 2015. https://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/. Accessed May 29, 2019. **[STEP 5]**

CME

(No) Shot to the heart: Alcohol abstinence reduces atrial fibrillation burden in drinkers

Voskoboinik A, Kalman JM, De Silva A, et al. Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med*. 2020;382(1):20-28.

DOI 10.1097/EBP.0000000000001360

This was a multicenter, prospective, open-label, randomized controlled trial (N=140) from six sites in Australia. Inclusion criteria: adults 18 to 85 years old; consume >10 standard alcohol-containing drinks per week; have paroxysmal or persistent atrial fibrillation (AF); and in sinus rhythm at time of enrollment (with or without antiarrhythmic therapy). Exclusion criteria: alcohol dependence or abuse; severe left ventricular systolic dysfunction (ejection fraction <35%); and clinically significant noncardiac illnessor coexisting psychiatric disorder.

Primary outcomes during the six-month study: recurrence of AF and total AF burden (percentage of time in AF). After a four-week run-in period, patients were randomized to two groups, an abstinence and a control group. Comprehensive rhythm monitoring occurred for all patients after randomization. Alcohol consumption was reported using a weekly alcohol diary, supplemented with a visual guide showing pictures of standard alcohol drinks, and random urine testing for ethyl glucuronide (an alcohol metabolite).

Patients (85% men) were randomized evenly into control and abstinence groups. The abstinence group decreased their alcohol consumption from 16.8 drinks a week to 2.1 drinks a week. The control group reduced their intake from 16.49 drinks a week to 13.2 drinks a week. AF recurred in 53% of the abstinence group and 73% in the control group, with a longer period before recurrence in the abstinence group than in the control group (hazard ratio 0.55; 95% CI, 0.36–0.84; number needed to treat=5). AF burden (percentage of time in AF) was also lower in the abstinence group (0.5%; interquartile range [IQR] 0.0–3.0) than in the control group (1.2%; IQR 0.0–10.3; P=.01).

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching UpToDate, Dynamed, American Heart Association, and American College of Cardiology, with the terms (drinking, alcohol, alcohol use, AF, recurrence, and abstinence) to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: Patients with paroxysmal or persistent AF can reduce their time in AF, as well as their overall recurrence of AF, by decreasing their alcohol consumption by half or more. Providers can use this evidence to support counseling patients with AF about reducing alcohol consumption. Approximately one of every five patients who reduce their alcohol consumption will benefit.

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

To complete the CME activity for this article, please go to: https://cme.lww.com/public/modules/15125

Stroke survivors may do better with aerobic conditioning

Regan EW, Handlery R, Beets MW, Fritz SL. Are aerobic programs similar indesign to cardiac rehabilitation beneficial for survivors of stroke? A systematic review and meta-analysis. *J Am Heart Assoc*. 2019; 8(16):e012761.

DOI 10.1097/EBP.0000000000001118

This systematic review and meta-analysis of 19 pre/post test trials of varying study design, including randomized controlled trials (12) and cohort studies (7), was conducted

to determine if cardiac rehabilitation-type programs help stroke survivors. Eligible studies delivered group-based aerobic exercise therapy sessions to adult stroke survivors. There were 485 participants in qualified studies, which included those from 13 countries, and in all but one study, they had independent ambulation with or without an assistive device. Sessions were delivered over varying timelines ranging from 8 to 18 weeks with the number of sessions varying from 18 to 36. Each study had at least one measure of aerobic capacity (time limited walking tests, walking speed, or VO2 peak), and the standard mean differences of the summary effect sizes were combined into a composite aerobic capacity measure for meta-analysis (Hedges g). These survivors showed significantly improved aerobic capacity with a composite variable effect size of 0.38 (95% CI, 0.27–0.49). Specifically, the six-minute walking test showed an improvement in 53.3 m (95% CI, 36.8–69.8) on average from baseline. This means these survivors could functionally advance in their mobility from limited in the community to unlimited in the community, such that now they could ambulate in shopping trips, not just walk to the mailbox. Follow-up data in these studies were sparse and inconclusive. Adverse effects were not reported in this summary.

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

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

Bottom line: Although the included studies in this review found that stroke survivors gain significant initial improvement with enhanced aerobic and walking capacity, definite recommendations cannot be made based solely on this review due to its significant limitations, including variable study designs, lack of control group inclusion, limited follow-up data, and no reporting of adverse effects.

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Intracervical block decreases severe pain during insertion of levonorgestrel-releasing intrauterine system in nulliparous women

De Nadai MN, Poli-Neto OB, Franceschini SA, et al. Intracervical block for levonorgestrel-releasing intrauterine system placement among nulligravid women: a randomized double-blind controlled trial. *Am J Obstet Gynecol*. 2020; 222(3):245.e1–245.e10.

DOI 10.1097/EBP.0000000000001186

This double-blinded randomized control trial at two Brazilian university hospitals randomized 302 nulliparous women between the ages of 18 and 45 years old who desired first-time placement of levonorgestrel-releasing intrauterine device (LNG-IUS) to receive an intracervical block with 3.6 mL of 2% lidocaine (72 mg), sham intracervical block, or no intervention before tenaculum placement and LNG-US insertion. Primary outcomes aimed to compare pain at insertion of LNG-IUS, whereas secondary outcomes measured pain with tenaculum placement, ease of insertion as assessed by inserting health care provider, and patient's overall experience with the procedure. Patients were excluded if they had medical conditions considered contraception risk categories three or four per the World Health Organization's medical eligibility criteria, allergies or contraindications to lidocaine, history of chronic pelvic pain, abnormalities or surgery of cervix, illicit drug or alcohol use, psychiatric conditions, or use of medications that could interfere to with pain perception. Interventions were completed before tenaculum placement, with outcomes assessed immediately after tenaculum placement, immediately after LNG-IUS placement and again at 24 hours via telephone survey. Severe pain at LNG-IUS insertion was less frequent in the intracervical block group (26.5% vs sham: 59.4% vs no intervention: 50.5%, $P<.0001$). Severe pain after tenaculum placement was less frequent in the intracervical block group (2% vs sham: 30.2% vs no intervention 15.2%, $P<.0001$). Ease of insertion was not statistically different ($P=.35$) between the three groups. Pain was rated by patients

as "lower than expected" in the intracervical block group (62.8% vs sham: 25% versus no intervention: 36.7%, $P<.0001$). Twenty-four hours after the procedure, 5.1% of intracervical block group patients reported that they would not be willing to undergo the procedure again, which was less than the sham (18.2%) and no intervention (10%) groups ($P=.01$).

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here.[1] An additional literature search was conducted by searching UpToDate with the terms intracervical block, paracervical block, IUD placement, IUS placement, and intrauterine contraception (IUC) placement to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: Intracervical block with 3.6 mL of 2% lidocaine reduces severe pain with LNG-IUS placement in nulliparous women without prior IUC as compared with sham intracervical block and no intervention. Severe pain with tenaculum placement was also decreased in women receiving intracervical block. Ease of LNG-IUS insertion was similar among the three study groups.

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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 US Air Force Medical Department, the Air Force at large, or the Department of Defense.

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Chlorthalidone superior to hydrochlorothiazide to treat hypertension: maybe not!

Hripcsak G, Suchard MA, Shea S, et al. Comparison of cardiovascular and safety outcomes of chlorthalidone vs hydrochlorothiazide to treat hypertension. *JAMA Intern Med*. 2020; 180(4):542–551.

DOI 10.1097/EBP.0000000000001186

This large-scale retrospective, observational, cohort study of 730,225 patients (61% women) compared acute myocardial infarction, hospitalization for heart failure, ischemic or hemorrhagic stroke, and composite cardiovascular disease outcomes among first-time users of antihypertensive monotherapy with either chlorthalidone or hydrochlorothiazide (HCTZ). The authors used complex computer-generated risk propensity scores to estimate hazard ratios for both medications. Exclusion criteria were known prior exposure to any hypertension therapies, initiation of other hypertension treatment within seven days after starting either above medications, known prior primary outcomes, and less than one day at risk. Patients required observation for more than 365 days on the electronic health database before initiation of antihypertensive medication. A total of 51 safety outcomes were studied. Of the 730,225 patients, 36,918 were given chlorthalidone and had 149 composite outcome events and 693,337 were given HCTZ and had 3,089 events. No significant difference in primary outcomes were found between the medications (hazard ratio [HR] 1.00; 95% CI, 0.85–1.17). Chlorthalidone was associated with a significantly higher risk of hypokalemia (HR, 2.72; 95% CI, 2.38–3.12), hyponatremia (HR, 1.31; 95% CI, 1.16–1.47), hypomagnesemia (HR of 1.57; 95% CI, 1.16–2.12), acute renal failure (HR, 1.37; 95% CI, 1.15–1.63), chronic kidney disease (HR, 1.24; 95% CI, 1.09–1.42), and type 2 diabetes mellitus (HR, 1.21; 95% CI, 1.12–1.30). Chlorthalidone was associated with a significantly lower risk of diagnosed abnormal weight gain (HR, 0.73; 95% CI, 0.61–0.86). These results are contrary to the current American Heart Association (AHA)/American College of Cardiology (ACC) hypertension guideline recommendation to use chlorthalidone over HCTZ as the choice of thiazide diuretic because of improved cardiovascular outcomes and lack of safety concerns between the two medications.

Methods

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

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

Bottom line: The findings of this study call into question the ACC/AHA guideline recommendation of chlorthalidone over hydrochlorothiazide because of superior cardiovascular outcomes. In addition, this investigation reveals a potentially significant increased risk of harm with regard to electrolyte abnormalities and renal dysfunction with the use of chorthalidone compared with HCTZ for initial therapy for primary hypertension. However, despite the AHA/ACC guideline recommendations, the majority of thiazide diuretic prescriptions in this country remain for HCTZ.

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

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Pregnant with back pain? Try OMT

Osteopathic manipulative treatment for low back and pelvic girdle pain during and after pregnancy: a systematic review and meta-analysis

Franke H, Franke JD, Belz S, Fryer G. "Osteopathic Manipulative Treatment for Low Back and Pelvic Girdle Pain during and after Pregnancy: A Systematic Review and Meta-Analysis." *J Bodywork Mov Ther*. 2017; 21: 752–762. DOI 10.1097/EBP.0000000000001056

KEY TAKEAWAY: Osteopathic manipulative treatment (OMT) provided moderate improvement (over a combination of no treatment, usual care, and sham treatment) in both pain and function in pregnant and postpartum patients with low back pain (LBP) and pelvic girdle pain.

STUDY DESIGN: Systematic review and meta-analysis of randomized controlled trials (RCTs).

LEVEL OF EVIDENCE: Step 1.

BACKGROUND: Low back pain and pelvic pain are common complaints during pregnancy and postpartum. OMT is commonly performed for these conditions, but evidence for its efficacy is uncertain. This study evaluated the effectiveness of OMT for improvement in pain and function in pregnant and postpartum patients with LBP or pelvic pain.

PATIENTS: Patients—Pregnant and postpartum patients with LBP or pelvic pain, adults >18 years.

INTERVENTION: Intervention—OMT (any combination of techniques, but performed by osteopaths).

CONTROL: Comparison—Usual care, sham treatment, or no treatment.

OUTCOME:

- Primary outcome: improvement in pain on the visual analogue scale (VAS), number rating scale (NRS), or the McGill Pain Questionnaire and functional status using the Roland-Morris Disability Questionnaire, Oswestry Pain Questionnaire, Pelvic Girdle Pain Questionnaire, or other instrument.
- Secondary outcome: adverse events.

METHODS BRIEF DESCRIPTION:

- Literature search in 2016 of numerous databases included only RCTs, published or unpublished; no language restriction.
- Studies assessed for heterogeneity via I^2, bias via the Cochrane Risk of Bias tool, and evidence quality via GRADE approach.
- Effect sizes calculated as well as mean difference (MD) and standardized mean difference for outcomes.
- Authors adhered to PRISMA guidelines.

INTERVENTION (# in the group)

- Five antepartum studies, n=248
- Three postpartum studies, n=90

COMPARISON (# in the group)

- Five antepartum studies, n=429
- Three postpartum studies, n=90

FOLLOW-UP PERIOD: Postpartum ranged from 3 to 24 months.

RESULTS:

- Primary outcomes
  - OMT was more effective than comparison groups (3 untreated, 2 usual care, 2 sham) in decreasing LBP during pregnancy (7 studies, n=677; MD, –16.7; 95% CI, –31.8 to –1.7).
  - OMT was more effective than comparison groups (3 untreated, 2 usual care, 2 sham) in improving functional status during pregnancy (7 studies, n=677; MD, –0.5; 95% CI, –0.93 to –0.07).
  - OMT was more effective than comparison groups (3 untreated) in decreasing LBP postpartum (3 studies, n=180; MD, –38.0; 95% CI, –46.7 to –29.2).
  - OMT was more effective than comparison groups (3 untreated) in improving functional status postpartum (3 studies, n=180; MD, –2.1; 95% CI, –3.0 to –1.2).
- Secondary outcomes
  - No adverse events reported.

LIMITATIONS:

- Small sample sizes
- Lack of high-quality RCTs
- Minimal data on adverse events
- High level of heterogeneity

EBP

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The authors declare no conflicts of interest.

An apple (watch) a day for diagnosing a-fib today

Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation

Marco V Perez, Kenneth W Mahaffey, Haley Hedlin, et al. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. N Engl J Med 2019; 381: 1909–17 DOI 10.1097/EBP.0000000000001095

KEY TAKEAWAY:
- The probability of receiving an irregular pulse notification while wearing an Apple Watch is low. Among patients with an irregular pulse notification who underwent evaluation, 34% had atrial fibrillation.

STUDY DESIGN:
- A prospective, single group, open-label, siteless pragmatic study.

LEVEL OF EVIDENCE: STEP 3.

BRIEF BACKGROUND INFO: Many people use technology and apps in their daily lives. Technology companies are offering monitoring of various biometrics. Little is known whether personal monitoring devices, such as the Apple Watch, can detect arrhythmias.

PATIENTS: U.S. adults 22 years and older.
INTERVENTION: Apple iPhone and Watch with an irregular pulse notification algorithm app.
CONTROL: None.
OUTCOME: Formal diagnosis of a-fib.

METHODS BRIEF DESCRIPTION: Patients were enrolled between November 29, 2017, and August 1, 2018. Inclusion criteria were as follows: living in the US, ownership of an Apple Watch and iPhone, and English proficiency. Exclusion criteria were as follows: previous a-fib diagnosis and taking oral anticoagulants. After obtaining consent, an irregular pulse notification app was activated.

Participants wore an Apple Watch and were alerted if it detected an irregular pulse. They would be prompted to initiate a telemedicine visit. Urgent, symptomatic patients were prompted to seek care. Nonurgent patients were mailed an EKG patch which was mailed back and evaluated.

Participants who received an irregular pulse notification were asked to complete a survey at 90 days. All participants were directed to a web-based end of study survey.

INTERVENTION (# IN THE GROUP): 450.
COMPARISON (# IN THE GROUP): None.

FOLLOW UP PERIOD: Median monitoring period 117 days.

RESULTS:
- Of the 419,297 initial participants, 2,161 (.52%) received an irregular pulse notification. After 1,216 participants did not initiate a first visit and others were excluded, 450 used and returned EKG patches for analysis.
- Of those participants who returned a patch, 34% were found to have a-fib.
- Of the 2,161 participants who received an irregular pulse notification, 64% returned the 90-day survey, which indicated 57% contacted a health care provider outside the study, 28% were prescribed a new medicine, and 36% were recommended to have additional testing.

LIMITATIONS:
- Limitations included no direct physical contact between researchers and participants, and a large number of participants were lost to follow-up. The study relied on participants' self-reported data on preexisting conditions and subsequent diagnosis and medical management. EBP

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The author declares no conflicts of interest.

A steroidal impact

Controlled trial of budesonide-formoterol as needed for mild asthma

Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med*. 2019; 380(21):2020–2030. DOI 10.1097/EBP.0000000000001137

KEY TAKEAWAY: In patients with mild asthma, the use of as-needed budesonide-formoterol was superior to the use of as-needed albuterol in the prevention of asthma exacerbations.
STUDY DESIGN: Multisite, randomized, open-label, controlled trial
LEVEL OF EVIDENCE: Step 2

BACKGROUND: The frequency of exacerbations in patients with mild asthma has a significant impact on patients' quality of life. Treatment with inhaled glucocorticoids reduces the risk of exacerbations; however, many patients do not want to take medications when symptoms are mild or intermittent. Some double-blind randomized controlled trials have shown efficacy of as-needed budesonide-formoterol as reliever therapy; however, they lack external validity in how this treatment option translates into clinical practice.

PATIENTS: Adults 18 to 75 years old with asthma
INTERVENTION: Budesonide-formoterol
CONTROL: 1) Albuterol as-needed 2) Budesonide plus albuterol as-needed
OUTCOME: Primary: Annualized rate of asthma exacerbation
SECONDARY: The number of exacerbations, number of severe exacerbations, risk of exacerbation, and Asthma Control Questionnaire 5 Scores (ACQ-5), adverse events

METHODS: Patients included adults 18 to 75 years old (mean age 35–36 years old), with reported history of asthma diagnosed by a physician, being treated solely with as-needed short-acting beta-agonist over the past three months, which was used on at least two occasions but on average two or fewer occasions per day over the previous month. Each participant was randomly assigned to one of three groups: as-needed budesonide-formoterol (200 μg of budesonide and 6 μg formoterol and one inhalation as-needed), albuterol as-needed (100 μg two inhalations from metered-dose inhaler), or budesonide (200 μg, 1 inhalation twice daily scheduled) plus albuterol as-needed (100 μg 2 inhalations via MDI). Everyone was aware of treatment group assignments. Patients were provided with a log to keep track of any systemic steroid use or urgent medical visit, and an asthma action plan describing when to seek medical care. The inhalers that were dispensed during the trial had electronic inhaler usage monitors. Patients had seven trial visits over 52 weeks. Analysis was by intention to treat.

INTERVENTION (# IN THE GROUP): 220.

COMPARISON (# IN THE GROUP): 1) Albuterol as needed: 223, 2) Budesonide plus albuterol as needed: 225.

FOLLOW UP PERIOD: 52 weeks.

RESULTS:
- Budesonide-formoterol vs albuterol PRN group:
- Asthma exacerbation per patient per year was lower: absolute rate (AR) 0.195 versus 0.400; relative rate (RR) 0.49 (95% CI, 0.33–0.72; $P<.001$; number needed to treatT=5)
- Risk of exacerbation was lower (hazard ratio [HR] 0.46; 95% CI 0.29–0.73)
- Number of severe exacerbations was lower (9 vs 23, RR 0.40; 95% CI, 0.18–0.86)
- Budesonide-formoterol vs budesonide plus albuterol PRN:
- Asthma exacerbation per patient per year did not show significant difference (AR 0.195 vs 0.175; RR 1.12, 95% CI 0.75–1.79; $P=.65$)
- Risk of exacerbation did not differ (HR 0.93; 95% CI 0.55–1.57)
- Number of severe exacerbations was lower (9 vs 21, RR 0.44; 95% CI, 0.20–0.96)
- ACQ-5 scores were higher (mean difference 0.14; 95% CI, 0.05–0.23)

LIMITATIONS:
Patients and evaluators were not blind to treatment, <20 pack-year smokers included, industry funded study, location limited to New Zealand, United Kingdom, Italy, and Australia. EBP

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Is prednisolone an effective treatment of acute alcoholic hepatitis?

CASE PRESENTATION

A 41-year-old woman with a history of severe alcohol use disorder and decompensated cirrhosis with ascites was admitted to the hospital for concern for alcohol withdrawal and found to have acute alcoholic hepatitis. Her last drink of alcohol was 12 hours before admission, and she has a history of withdrawal seizures. Her Maddrey Discriminant Function score was 31.5 and Model for End-stage Liver Disease Score was 16 on admission. Given this patient presented with acute alcoholic hepatitis, would prednisolone be a beneficial treatment?

DOI 10.1097/EBP.0000000000001323

Bottom line

Prednisolone for the treatment of acute alcoholic hepatitis does not seem to reduce short-term (28 days to 3 months) mortality based on low-certainty evidence and may lead to higher risk of infection. However, consensus guidelines for alcoholic liver disease still recommend considering treatment with prednisolone in patients with severe alcoholic hepatitis (Maddrey Discriminant Function [MDF] score ≥32, with or without hepatic encephalopathy) and no contraindication to steroids.

Review of evidence

A 2019 systematic review and meta-analysis of 16 randomized controlled trials (RCTs; published from 1971 to 2015, with majority based in the United States) evaluated the benefits and harms of steroids in alcoholic hepatitis.[1] The three primary outcomes considered in the review were all-cause mortality, health-related quality of life, and serious adverse events. In the trials reviewed, oral prednisolone or IV methylprednisolone (with oral equivalents ranging from 0.5 mg/kg/d to 1,250 mg/d) were compared with placebo or no intervention in patients with a clinical or biochemical diagnosis of acute alcoholic hepatitis. Patients had various stages of alcohol-related liver disease. In a meta-analysis of 15 trials with 1,861 patients, prednisolone administration did not significantly improve all-cause mortality (risk ratio [RR] 0.90; 95% CI, 0.70–1.2; I^2=47%). The small number of trials and participants, poor trial designs, insufficiently reported randomization procedures, and inconsistency of the data with moderate heterogeneity led to low-certainty evidence because of the high risk of bias. This review also included a subgroup analysis of trial patients with mild alcoholic hepatitis compared with patients with severe alcoholic hepatitis. Severe alcoholic hepatitis was defined as a MDF score of ≥32 or presence of hepatic encephalopathy. No significant difference was noted in all-cause mortality among individuals with severe alcoholic hepatitis treated with prednisolone compared with placebo or no intervention (14 trials; N=1,679; RR 0.92; 95% CI, 0.73–1.2; I^2=37%). Likewise, all-cause mortality did not change with steroid therapy in patients with mild alcoholic hepatitis (4 trials; N=182; RR 1.0; 95% CI, 0.58–1.8; I^2=0%).

A 2015 randomized controlled trial, also included in the 2019 Cochrane review and reviewed separately due to large sample size, included pentoxifylline, and examination of harms of the intervention, came to similar conclusions regarding treatment with prednisolone in alcoholic hepatitis. This was a double-blind RCT with a two-by-two factorial design comparing treatment with pentoxifylline 400 mg three times daily and prednisolone 40 mg daily to placebo.[2] Patients had recent alcohol use and were all clinically diagnosed severe alcoholic hepatitis. In total, 526 patients received prednisolone (or prednisolone and pentoxifylline) and 527 patients did not receive prednisolone. Twenty-eight day mortality was not significantly different between these two groups despite a trend toward decreased mortality among participants who received prednisolone (OR 0.72; 95% CI, 0.52–1.01). The study also found that serious infection occurred more frequently in those receiving prednisolone versus those who did not receive prednisolone (13% vs 7%; P=.002; number needed to harm=17). The Cochrane Review made note of a 2018 meta-analysis which concluded that corticosteroids reduced risk of death in severe alcoholic hepatitis within 28 days after treatment.[3] However, this review did not assess risk of bias among the included trials, and enough data were not included in the meta-analysis to draw a reliable conclusion.

A 2010 consensus-based guideline (likely out of date) by the American Association for the Study of Liver Disease/American College of Gastroenterology recommended that patients with severe alcoholic hepatitis (MDF score ≥32, with or without hepatic encephalopathy) and no contraindications to steroids be considered for a four-week course of prednisolone (40 mg/d).[4] However, the 2018 European Association for the Study of the Liver clinical practice guideline also stated corticosteroids (prednisolone 40 mg/d or methyprednisolone 32 mg/d) should be considered in patients with severe alcoholic hepatitis to reduce short-term mortality.[5] However, they note that corticosteroids do not influence medium- to long-term survival.

CASE CONCLUSION

On admission to the hospital, she was not started on prednisolone for treatment of severe alcoholic hepatitis given her MDF score was not ≥32 and no signs of hepatic encephalopathy were noted. She was started on an alcohol withdrawal protocol and the addiction medicine service was consulted. By hospital day five, she was stable to discharge to an intensive outpatient rehabilitation program for people living with alcohol use disorder. EBP

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Is transcranial magnetic stimulation an effective treatment in patients with resistant depression?

EVIDENCE-BASED ANSWER

Transcranial magnetic stimulation (TMS) treatments modestly reduce depression symptoms compared with sham treatment in patients with treatment resistant depression. (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Repetitive TMS does not improve remission of depression compared with sham treatment in veterans with a high burden of comorbid posttraumatic stress disorder (SOR: **B**, single small RCT).

DOI 10.1097/EBP.0000000000001017

A 2019 systematic review and meta-analysis[1] evaluated 23 RCTs comparing the use of standard accepted protocols of TMS with sham transcranial magnetic treatments for depression symptoms in patients with treatment resistant depression. Treatment resistant depression was defined as having failed at least one adequate trial of an antidepressant medication. Nineteen studies used a unilateral treatment protocol (n=1,090) and four used a bilateral treatment protocol (n=172). Treatment range was 10 to 30 sessions with 20 to 75 trains/session of 2 to 8 seconds each. In all studies, sham treatment consisted of the stimulator probe placed in a nonstandard and presumed ineffective location with the same duration as treatment above. Median age of included patients ranged from 38 to 64 years and, 58% of patients were female. Almost all patients had unipolar depression (99.1%). The primary outcome was the Hamilton Rating Scale for Depression score before and at the end of the intervention. The Hamilton Rating Scale scores range 0 to 54 where a score less than seven indicates no depression and over 17 indicates severe depression, and a 3-point change indicates clinical response. Secondary analyses included measures of response (decrease in Hamilton Rating score of at least 3) and remission (Hamilton Rating scale decline to 7 or lower). Unilateral TMS improved the Hamilton Rating scale compared with sham treatment (19 studies, n=1,090; weighted mean difference [WMD] 3.4; 95% CI, 1.9–4.9). Bilateral TMS also improved the Hamilton Rating scale score compared with sham treatment (4 studies, n=172; WMD 2.7; 95% CI, 0.8–4.5). In analyses of secondary outcomes, both the pooled response rate (17 studies, n not given; 25.1% vs 11%; relative risk [RR] 2.0; 95% CI, 1.3–3.2; number needed to treat [NNT]=9) and pooled remission rates (13 studies, n not given; 16% vs 5.7%; RR 2.3; 95% CI, 1.5–3.6; NNT=7) for unilateral TMS were better than those of sham treatment. For bilateral TMS, the pooled response rate (25% vs 6.8%; RR 3.6; 95% CI, 1.9–6.8; NNT=6) and remission rate (17% vs 2%; RR 5.5; 95% CI, 2.0–15.6; NNT=7) were better than those of sham treatment. Limitations included heterogeneity in the sham treatment protocols.

A subsequent RCT[2] compared repetitive TMS (cycles of 4,000 pulses per session, up to 30 sessions delivered over five to 12 days) with sham TMS in treatment-resistant major depression in veterans (N=164, 81% male; 77% White; 49% with comorbid PTSD). The primary outcome was remission of depression at 24 weeks, defined as a score of 10 or less on the Hamilton Rating Scale for Depression. There was no significant difference in remission of depression in the repetitive TMS group compared with sham treatment (41% vs 37%; odds ratio 1.2; 95% CI, 0.6–2.3). Remission rates were better for veterans in the repetitive TMS group who did not have comorbid PTSD (n=41; 49% vs 43%; no *P* value given). EBP

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Is behavioral therapy a more effective treatment for primary insomnia than pharmacotherapy?

EVIDENCE-BASED ANSWER

Behavioral therapy (stimulus control therapy and sleep restriction) can improve outcomes like sleep latency, number of awakenings, and total sleep time comparable with pharmacotherapy (SOR: **B**, meta-analysis not limited to randomized controlled trials [RCTs]). Cognitive behavioral therapy for insomnia is more effective for treating insomnia than benzodiazepines in the long term (SOR: **B**, systematic review of small RCTs).

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A 2002 meta-analysis (21 prospective studies; n=470) compared the effectiveness of pharmacotherapy and behavior therapy for persistent insomnia among adults with primary insomnia for at least one month.[1] Study samples included males and females with a mean age of 47.2 years and a mean length of treatment of two weeks for pharmacotherapy and five weeks for behavioral therapy. The authors excluded studies if they included patients with psychiatric and general medical conditions, or patients who were not withdrawn from hypnotic medications before entering the trial. In all studies, behavioral therapy was defined as stimulus control therapy (teaching patients to use the bed only for sleep) with or without sleep restriction (setting strict limits on bedtime with the goal of establishing solid periods of sleep over time). Two studies used sleep restriction alone, and four studies combined stimulus control and sleep restriction. Pharmacotherapies included flurazepam, quazepam, triazolam, zolpidem, lorazepam, midazolam, and zopiclone. The outcomes measured were sleep latency, total sleep time, and the number of awakenings as measured by sleep diaries. Pharmacological and behavioral treatment reduced sleep latency in both groups (30% and 43%, respectively). Although no *P*-value was calculated for mean changes in sleep outcomes, the mean effect sizes (measure of change in standard deviation units) for all outcomes for pharmacotherapy and behavior therapy were 0.87 and 0.96, indicating overall similar efficacy for both groups. Limitations of this review included reliance on sleep diaries and study results were pooled, so individual pharmacological therapies could not be assessed.

A 2012 systematic review (n=294) analyzed five published randomized controlled trials that compared cognitive behavioral therapy (CBT) for insomnia to Food and Drug Administration (FDA)-approved prescription or nonprescription medications used to treat insomnia. The locations of the studies were Norway,

TABLE. Cognitive behavioral therapy (CBT) for insomnia versus prescription medications for insomnia

Medication	N	Outcome	Outcome measure; P value (CBT vs medication)
Short-term data (≤8 weeks)			
Zopiclone	46	Total wake time	–56.4 min vs –3.9 min; $P<.001$
Zolpidem	63	Sleep latency	–33.8 min vs –12.8 min; $P<.05$
Zolpidem	63	Sleep efficiency	17.3% vs 2.1%; $P=.007$
Temazepam	77	Sleep time	21.6 min vs 66.5 min; $P<.004$
Long-term data (8+ weeks)			
Triazolam	78	Sleep latency	–45 min vs 21 min; $P<.01$

USA, China, and Canada. Patients 18 years old and older diagnosed with chronic insomnia per Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria were included in the review. The five studies only used prescription benzodiazepines and other gamma aminobutyric acid (GABA) agonists.[2] In these studies, CBT for insomnia consisted of establishing a learned association between bed and sleeping through stimulus control, sleep restriction, and cognitive restructuring. Quantitative sleep outcomes measured were sleep latency, wake after sleep onset, sleep efficiency, total sleep time, and total wake time with at least two measures tabulated from each study. Outcomes were measured both immediately after treatment and then at the latest reported date, which ranged from eight weeks to two years after initiation of treatment. All trials used sleep diaries, and all but one used polysomnography or actigraphs to objectively measure sleep outcomes. The report of adverse events in all the trials was limited. Nonbenzodiazepine pharmacology was compared with CBT-I therapy in two of the five studies. When compared with zopiclone, CBT for insomnia had a greater decrease in total wake time as measured with polysomnography. Similarly, CBT for insomnia, when compared with zolpidem, had greater decreases in sleep latency and greater sleep efficiency as measured by sleep diary. Three of the five studies analyzed benzodiazepines. Patients reported greater sleep time on temazepam compared with CBT, measured by sleep diary, and confirmed with polysomnography, but in a similar study in 1999, there was no significant difference in total sleep time between the two groups. Finally, triazolam versus CBT for insomnia found no significant difference in sleep latency and total sleep in the short term. However, when used for 8+ weeks, CBT had a greater effect on sleep latency than triazolam (see **TABLE**). The effects of CBT for insomnia appear to be sustained over time, whereas the effects of drug therapy decline. One of the limitations is that these studies were not double-blinded. EBP

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In patients who have multidrug-resistant, gram-negative bacterial infections, does polymyxin B have less renal toxicity than colistimethate?

EVIDENCE-BASED ANSWER

Polymyxin B has less renal toxicity than colistimethate in patients with drug-resistant, gram-negative infections (SOR: **B**, meta-analysis of cohorts and single cohort). Nephrotoxicity also presents earlier in patients treated with colistimethate compared with polymyxin B (SOR: **B**, single cohort).[1]

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A meta-analysis of four retrospective and one prospective cohort studies (N=1,103) assessed the risk of developing nephrotoxicity in patients treated with colistimethate and polymyxin B for multidrug-resistant, gram-negative infections.[1] Baseline renal function of patients varied with some studies excluding those on dialysis entirely and others with up to 18% on dialysis. The majority of studies had at least 75% of patients in the intensive care unit and with treatment lasting around 10–12 days. Colistimethate was most commonly at around 4.0 mg/kg and polymyxin B at around 2.0 mg/kg. Nephrotoxicity was defined using RIFLE criteria (Risk, Injury, Failure, Loss of kidney function, and End stage renal disease) in all but two studies, with the other studies

using similar guidelines. Potential confounders included differences in patient comorbidities, severity of infection, dosing of antibiotic, site of infection, surgical control of the infection, and bacterial virulence. After adjusting for the above, nephrotoxicity presented more frequently in patients treated with colistimethate than in patients treated with polymyxin B, with greater irreversible kidney damage sustained in colistimethate-treated patients (hazard risk 2.2; 95% CI, 1.4–3.3).

The largest retrospective study (N=225) in the above meta-analysis was a multicenter cohort comparing toxicity rates between treatment with colistimethate and polymyxin B in patients with a gram-negative bacterial infection.[2] Patients with underlying kidney disease were excluded. Doses were given according to ideal body weight with colistimethate (n=121) dosed at 4.6 mg/kg and polymyxin B (n=104) dosed at 1.8 mg/kg; treatment follow-up was not adequately specified. The primary outcome measured was kidney function with correlated RIFLE criteria, whereas secondary outcomes included time to manifestation of nephrotoxicity and hospital mortality. The development of nephrotoxicity was significantly more common in patients receiving colistimethate treatment than in the polymyxin B group (55% vs 21%, $P<.003$). Nephrotoxicity also presented much earlier in the colistimethate group compared with the polymyxin B group (~5 vs ~15 days, $P=.003$). No significant difference was noted in overall hospital mortality between the two groups. EBP

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Compared with immediate antibiotic prescribing, does delayed antibiotic prescribing decrease patient satisfaction?

EVIDENCE-BASED ANSWER

Overall, patient satisfaction with delayed antibiotic prescriptions is equivalent to that with immediate antibiotic prescriptions in upper respiratory infections. Delayed antibiotic prescribing is preferred compared with no prescription at the initial encounter (SOR: **A**, systematic review and meta-analysis of randomized controlled trials). In some settings, patients with respiratory infections may favor wait-and-see prescriptions to immediate antibiotic prescriptions (SOR: **C**, patient questionnaire survey).

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A 2017 systematic review of 11 randomized controlled trials (N=2,487) evaluated patient satisfaction with varied approaches to antibiotic prescribing in multiple forms of upper respiratory illnesses for both adults and children.[1] Patients presented to ambulatory clinics with acute otitis (3 trials), strep pharyngitis (3 trials), cough (2 trials), the common cold (1 trial), or a combination of several upper respiratory infections (1 trial). Three trials enrolled only children, three trials enrolled only adults, and the remaining five trials enrolled all age groups. Patients were immediately prescribed antibiotics, had antibiotics prescribed after a delay of two, three, or seven days, or not prescribed antibiotics at initial appointment. Patient satisfaction was measured on 4- or 6-point Likert scales, which were converted to binary responses of satisfied/unsatisfied and represented as odds ratios (ORs). Compared with immediate prescription, no significance difference was noted in patient satisfaction in the delayed prescribed group (6 trials, n=1,439; OR 0.65; 95% CI, 0.39–1.1). However, satisfaction rate was significantly higher with

delayed prescribing compared with no initial antibiotics prescribed at all (4 trials, n=1,048; OR 1.5; 95% CI, 1.1–2.1).

A 2011 questionnaire survey of 413 Norwegian patients and their 49 general practitioners explored general practitioners' use of delayed antibiotic prescribing ("wait-and-see prescriptions") and patients' willingness to use this approach.[2] Providers went to a one-day seminar that included information on how to use delayed antibiotic prescribing for respiratory tract infections; they then enrolled eligible patients as they felt appropriate. A total of 413 patients were offered participation, 81 were withdrawn because of a lack of physician response, five patients declined participation, 17 did not meet proper inclusion criteria, and six patients failed to report if they eventually used antibiotics. The response population included 100 patients 15 years old or less, 180 patients 16 to 59 years old, and 24 patients 60 years old or older. Patients received an antibiotic prescription, instructions regarding when and how they could use their prescription, a survey, and a stamped envelope to send the survey back at an interval determined by their provider. Patients were enrolled for sinusitis (33%), otitis (21%), upper respiratory symptoms (20%), lower respiratory infection (14%), tonsillitis (8%), and other infection (4%). Of the 304 responding patients, 46% reported taking the antibiotic. Of responding patients, 89% stated they would prefer to receive a wait-and-see antibiotic prescription in the future, 3% would prefer an immediate antibiotic prescription, and 8% were uncertain. The study was limited by possible selection bias; participants received a "scratchcard" as a reward for agreeing to participate, although the authors did not identify the value of this reward; providers received a gift card after enrolling 10 patients in the study (average provider enrolled 8.5 patients), though the authors did not identify the value of this reward, either. Additional limitations of this study include lack of randomization, blinding, or a control group, and much of the survey data collected were subjective in nature. EBP

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How do outcomes compare for planned vaginal birth versus planned cesarean delivery for term breech presentation?

EVIDENCE-BASED ANSWER

Term breech vaginal delivery is associated with increase in perinatal morbidity and mortality compared with a planned cesarean section; however, the absolute risk remains relatively low (0.3 vs 0.05%; number needed to harm [NNH] 400; SOR: **A**, meta-analysis of primarily cohort studies). Compared with cesarean delivery, vaginal breech delivery is also associated with higher risk of a five-minute Agar score <7 (NNH=48), fetal neural injury (NNH=67), and infant birth trauma (NNH=189; SOR: **A**, meta-analysis of primarily cohort studies). A lower risk of maternal morbidity is associated with planned vaginal delivery (number needed to treat=167; SOR: **B**, meta-analysis of randomized controlled trials). Physicians can use these numbers for informed decision-making with their patients.

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A 2015 meta-analysis evaluated three randomized controlled trials (RCTs; N=2,396) regarding outcomes of planned vaginal delivery versus planned cesarean delivery for term breech presentation.[1] Of the women planning vaginal delivery, 45% had caesarian deliveries and 91% of the women planning to have caesarian delivery did have caesarian deliveries. All pregnancies were singleton breech deliveries. Studies included only frank breech presentation,

only non-frank breech presentation, and both frank and non-frank presentation. Two of the studies used over 36 weeks' gestational age and the third study used over 37 weeks' gestational age as the minimum gestational age. Estimated fetal weight for randomization was required to be 2,500 to 3,800 g in one study, 2,000 to 4,000 g in another study, and under 4,000 g in the third study to be eligible. Hyperextension of the fetal head, fetal anomalies, and contraindication for vaginal delivery or indication for cesarean delivery were exclusion factors from participation. Overall, planned caesarean delivery resulted in decreased perinatal and neonatal death (excluding fatal anomalies) compared with vaginal delivery for breech presentation (3 studies; n=2,388; risk ratio [RR] 0.29; 95% CI, 0.10–0.86; number needed to harm [NNH]=125), although increased maternal morbidity in the short term was observed for planned caesarean delivery compared with vaginal breech delivery (3 studies, n=2,396; RR 1.3; 95% CI, 1.03–1.6; NNH=167). Limitations of this review included suboptimal randomization in two trials and no blinding to the intervention, and design limitations were also noted in two of the three trials; the publication dates of the three studies evaluated (1980, 1983, and 2000) are also noted to be relatively old.

A 2015 meta-analysis evaluated 27 articles (N=258,953), 26 cohort studies, and one RCT, regarding perinatal morbidity and mortality for planned vaginal versus caesarean delivery for term breech presentation.[2] Trials enrolled only term singleton breech presentation; any cases with lethal congenital abnormalities, intrauterine fetal death, or caesarean delivery performed for another obstetric indication were excluded. One trial overlapped with the first meta-analysis above. For planned vaginal breech delivery, the risk of perinatal mortality was greater risk than with planned caesarean delivery (16 studies, n=235,536; 0.3 vs 0.05%; RR 4.6; 95% CI, 2.6–8.1; I^2=36%; NNH=400). The risk of fetal neurologic morbidity was greater in planned vaginal delivery compared with planned cesarean delivery (9 studies; n=29,937; 0.7% vs 0.1%; RR 2.6; 95% CI, 1.4–4.7; I^2=10%; NNH= 67); risk of birth trauma was more than four times greater in planned vaginal delivery (20 studies; n=127,152; 0.7% vs 0.17%; RR 5.0; 95% CI, 3.8–8.6; I^2=16%; NNH=189); five-minute Apgar score <7 was about five times more likely in planned vaginal delivery (23 studies; n=155,836; 2.4% vs 0.3%; RR 4.7; 95% CI, 3.6–6.0; I^2=61%; NNH=48); and the absolute risk of neonatal asphyxia was more than five times greater in the planned vaginal delivery group (9 studies, n=10,662; 3.3% vs 0.6%; RR 3.9; 95% CI, 2.7–5.8; I^2=9%; NNH=37). Several limitations of this meta-analysis included that most studies were retrospective and observational, which increased opportunity for bias. Large variation in sample size was noted among the studies, ranging from 162 to 100,667, thus smaller studies had little contribution to calculating the overall RR. EBP

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What are effective treatments for hyperhidrosis that is refractory to nonprescription treatments?

EVIDENCE-BASED ANSWER

Oxybutynin treatment reduces symptoms of primary hyperhidrosis (SOR: **B**, systematic review of randomized controlled trials [RCTs], nonrandom trials, and case reviews). Methantheline bromide also reduces axillary and palmer sweating (SOR: **B**, single RCT from systematic review). Topical glycopyrronium tosylate applied on a daily basis over four weeks reduces sweat production and symptom severity (SOR: **B**, two pooled RCTs).

DOI 10.1097/EBP.0000000000001167

A systematic review (N=364) of four RTCs, 14 controlled trials, and five case reviews examined the effect of oral anticholinergic medications on adults with primary

hyperhidrosis.[1] Patients (ages 18–66 years old) were included if they received a clear diagnosis of hyperhidrosis in the clinical setting. Patients with secondary hyperhidrosis and those using nonoral anticholinergic agents were excluded. Treatments evaluated included 10 to 20 mg oxybutynin (16 studies, n=2,351), glycopyrrolate (six studies, n=162), and methantheline bromide (1 study, n=267) daily for a minimum of four weeks. Outcomes measured were clinical improvement of hyperhidrosis and quality of life. Scoring systems used varied greatly, so results were only reported as percentage improvements compared with baseline. Follow-up was six months for oxybutynin, 10 years for glycopyrrolate therapy, and four weeks for methantheline. Compared with baseline or placebo groups, there was a significant improvement in both clinical symptoms (76% improvement, $P<.05$) and quality of life (74% improvement, $P<.05$) for patients treated with oxybutynin. There was a 41% reduction in axillary sweating and 16% reduction in palmar sweating for patients treated with methantheline bromide compared with placebo The results for glycopyrrolate were not quantifiable because of variable data. The most common side effect reported from oxybutynin therapy was dry mouth and appeared to be dose related.

Two pooled 2015 phase 3 RCTs (N=697) examined the effectiveness of topical glycopyrronium tosylate on patients aged nine years old or older with primary axillary hyperhidrosis.[2] Patients had an Axillary Sweating Daily Diary (ASDD) score of four at baseline, a Hyperhidrosis Disease Severity Scale of three or four at baseline, and a measured sweat production of at least 50 mg over five minutes in each axilla. Patients in the trials were randomized to receive either glycopyrronium (n=463) or placebo (n=234) daily for four weeks. The ASDD is a four-item questionnaire evaluating the impact of axillary hyperhydrosis on daily activities and ranges from scores of one to four, with higher scores indicating more impairment. Results from both identically ran trials were then pooled for analysis. There was a significant improvement in ASDD scores at four weeks in the treatment group compared with placebo (60% vs 28%, $P<.05$). When compared with baseline, patients treated with glycopyrronium had significantly greater sweat reduction compared with placebo (–108 vs –92 mg/5 minutes, $P<.001$). EBP

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Should hospitalized patients with liver disease and an elevated INR get pharmacological DVT prophylaxis?

EVIDENCE-BASED ANSWER

No. Using pharmacological agents such as unfractionated heparin or low-molecular-weight heparin in patients with cirrhosis and elevated international normalized ratio (INR) during hospitalization does not decrease the risk of developing deep vein thrombosis (DVT) (SOR: **B**, consistent evidence from two prospective cohorts).

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A 2017 retrospective cohort (N=300) analyzed the frequency of venous thrombotic events (VTEs) in cirrhotic patients with an elevated INR treated with DVT prophylaxis or low-molecular-weight heparin.[1] Cirrhotic patients who had an INR of 1.3 or greater and were hospitalized for greater than 72 hours were included. Patients were excluded if they had an active VTE, a bleeding event within 24 hours, or were recently prescribed anticoagulation medication. Participants were treated with subcutaneous heparin 5,000 U 2 to 3 times a day or 5,000 U dalteparin daily (n=152) or were withheld anticoagulation (n=148). VTE was considered in patients who were diagnosed

with DVT, pulmonary embolism, or who were given therapeutic anticoagulation who did not have atrial fibrillation, acute coronary syndrome, or percutaneous intervention during that hospitalization. No significant difference was found between the occurrence rate of VTE between the prophylaxis group and those who did not receive anticoagulation (risk ratio [RR], 2.7; 95% CI, 0.8–8.3), although the CI was wide.

A 2015 retrospective cohort (N=600) assessed the rate VTE in adult cirrhotic patients.[2] Patients were excluded if there was insufficient evidence of cirrhosis, clinical bleeding or VTE present at time of admission, or treatment of full-dose anticoagulation prior to admission. Prophylaxis consisted of subcutaneous heparin 5,000 U every eight or 12 hours or subcutaneous enoxaparin 40 mg. VTE prophylaxis was given in 296 (49%) of the admissions compared with 304 (51%) who did not receive prophylaxis. It should be noted that the prophylaxis group was significantly older (59 vs 55 years old; $P<.001$), had a lower mean INR (1.4 vs 1.7; $P<.001$), and a longer length of admission stay (9.6 vs 6.8 days; $P=.002$). Any new documented thrombosis involving lower extremity, upper extremity, visceral vein or pulmonary artery was considered an in-hospital VTE event. No significant difference in occurrence of VTE events was observed between the prophylaxis group and the untreated group (2.4% vs 1.7%; $P=.54$). Additionally, those who received prophylaxis had the same risk as those without treatment for a bleeding event while hospitalized (8.1% vs 5.5%; $P=.26$). EBP

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Can oral or vaginal probiotics taken prior to GBS testing prevent positive tests?

EVIDENCE-BASED ANSWER

Using oral probiotics to prevent Group B *Streptococcus* (GBS) colonization does not appear to be effective (SOR: **B,** randomized controlled trial [RCT]). The evidence is conflicting if oral probiotics eradicate GBS in patients who are known GBS positive (no SOR given). Evidence on vaginal probiotics is lacking.

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A 2019 RCT of pregnant patients (n=113) less than 25 weeks of gestation randomized patients to receive *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 daily oral probiotics to reduce Group B *Streptococcus agalactiae* (GBS) colonization during pregnancy. Patients were compared with placebo over a 12-week period.[1] The primary outcome was feasibility, and a secondary outcome was the rate of GBS colonization by rectovaginal swab at 35 to 37 weeks. No significant difference was observed in rates of GBS positivity between the probiotics group compared with the placebo (16% vs 21%; $P=.48$). This study was limited by the small sample size. It was noted that they were unable to enroll the desired number of patients as a result of the probiotic capsules expiring; therefore, the study was ultimately not powered to detect a difference.

A 2019 observational study evaluated the eradication of GBS in GBS-positive pregnant patients (n=57) with daily oral *Lactobacillus salivarius* CECT 7945 probiotics from 26 to 38 weeks of gestation[2]. Patients were separated into three groups (1 probiotic group and 2 placebo groups). All patients in the probiotic group (n=25) received daily probiotic. The placebo groups were divided into GBS-positive patients (n=14) and GBS-negative patients (n=18). The primary outcome was rates of GBS positivity measured by separate vaginal and rectal swabs. Among the GBS-positive group receiving probiotics, GBS-negative rates at 38 weeks by individual rectal and vaginal swab were 72% and 68%, respectively ($P<.05$ for each swab), whereas GBS status was

unchanged among the placebo groups, with all 14 patients remaining positive. Limitations of this study included no statistical analysis of GBS-negativity rates over the intervention period and small sample size. Additionally, no randomization of participants was done to study groups; all GBS-negative and GBS-positive patients receiving placebo had a previous infant with GBS sepsis.

A 2011 RCT evaluated a research method to study the causal relationship between probiotic use and GBS positivity in pregnant women.[3] GBS-positive pregnant patients (n=34) at 36 weeks of gestation were randomized to receive either daily oral probiotic *L rhamnosus* GR-1 or *L reuteri* RC-14, (n=21) or routine antenatal care (n=13). Patients took probiotics for three weeks or until delivery. Patients performed a self-swab for GBS after three weeks. The primary outcome was GBS colonization status assessed by vaginal swab. No difference was observed between the rates of negative GBS swabs among the intervention group compared with control (4/19 negative vs 3/13 negative; *P*=.7). This study was limited by only seven patients in the intervention group completing the full three-week course of probiotics. A subgroup analysis of patients completing at least 14 days of probiotics (n=16) also failed to identify a significant difference. Additional limitations included a small sample size with no power calculation and a relatively short duration of the intervention.

A 2016 RCT evaluated the relationship between daily probiotic use and GBS-positivity rates in pregnant patients (n=99) with positive GBS rectovaginal swabs at 35 to 37 weeks of gestation.[4] Patients were randomized to receive either daily oral probiotic strains *L rhamnosus* GR-1 and *L reuteri* RC-14 or placebo daily until delivery. The primary outcome was the rate of negative GBS rectovaginal swab at the time of admission for delivery. Among patients receiving probiotics, more patients had a negative GBS swab at admit compared with the control group (43% vs 18%; *P*=.007). This study was limited by a small sample size, although it was appropriately powered, as well as a short duration of intervention and no control for supplement use or nutritional status. EBP

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Do mediolateral episiotomies reduce incidence of third-/fourth-degree perineal lacerations when compared with standard midline episiotomy?

EVIDENCE-BASED ANSWER

No difference is noted in the rates of third- and fourth-degree lacerations when comparing routine with selective episiotomy nor when comparing mediolateral with midline episiotomy (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]), although cohort studies have concluded otherwise The American College of Obstetricians and Gynecologists states mediolateral episiotomies may be preferable because of an association between mediolateral episiotomies and injury to the anal sphincter complex (SOR: **C**, evidence-based practice guideline).

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A 2017 meta-analysis of 12 RCTs with 6,177 pregnant women compared selective versus

routine use of episiotomy.[1] The review included pregnant women over 16 years old without "severe medical or psychiatric conditions" between 28 and 40 weeks' gestation undergoing normal or assisted vaginal deliveries. They were sorted into groups of selective, when clinically indicated, and routine episiotomy. Most of the trials used mediolateral (10 studies) over midline episiotomy (2 studies). The primary outcome included severe perineal/vaginal trauma, infection, and pain. Severe perineal trauma was defined as third-degree and fourth-degree vaginal lacerations. Episiotomy rates in the selective group were 32% compared with 83% in the routine group. A subgroup analysis evaluated rates of severe perineal trauma (third- and fourth-degree lacerations). No difference was noted in severe perineal trauma between selective and routine midline episiotomy (2 trials, n=1,143; relative risk [RR] 0.74; 95% CI, 0.51–1.1) or between selective and routine mediolateral episiotomy (8 studies, n=4,834; RR 0.62; 95% CI, 0.37–1.04). When comparing rates between midline and mediolateral episiotomy, no difference was noted (RR 0.74 and RR 0.62; $P=.6$). The study was limited by possible publication bias because smaller studies that were included in the review showed higher rates of perineal trauma.

A 2007 prospective cohort study including 1,302 women analyzed the outcomes of selective midline and mediolateral episiotomies.[2] Pregnant women with singleton, low-risk pregnancies and cephalic presentations who delivered vaginally at term gestation were included. Patients undergoing midline versus mediolateral episiotomies were 28 years old versus 26 years old, gravity of 1.9 versus 1.7, gestational age 39 weeks, percentage of normal vaginal delivery of 89% versus 85%, percentage of forceps extraction of 5.7 versus 5.6, and percentage of vacuum extraction of 5.9 versus 9.6. The primary outcome was a severe perineal tear into the anal sphincter or rectum. Rates of severe perineal tears were higher in the midline over the mediolateral group (15 vs 7%; $P<.05$; RR 2.1; 95% CI, 1.5–3). Rates of other adverse outcomes for midline versus mediolateral episiotomies were measured, including dyspareunia (0% vs 15.8%, respectively) and wound infection (0% vs 0.002%). No difference was noted in the rate of blood loss, although blood loss was not objectively measured and was based only on visual inspection. The study was limited by significant loss to follow-up, making long-term outcomes difficult to assess.

A 2018 evidence-based practice bulletin from The American College of Obstetricians and Gynecologists (ACOG) reviewed prevention and management of obstetric lacerations.[3] This reported that midline episiotomies were a "strong independent risk factor for third-degree and fourth-degree lacerations" but it was difficult to determine the effects of mediolateral episiotomies. The committee released a recommendation that "if there is need for episiotomy, mediolateral episiotomy may be preferred over midline episiotomy because of the association of midline episiotomy with increased risk of injury to the anal sphincter complex; however, limited data suggest mediolateral episiotomy may be associated with an increased likelihood of perineal pain and dyspareunia" (level B recommendation, based on "limited or inconsistent scientific evidence"). EBP

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Is there a difference between aerobic exercise and resistance training for improved glucose control in patients with type 2 diabetes?

EVIDENCE-BASED ANSWER

Both resistance training and aerobic exercise result in small to moderate improvements in HbA1c levels in patients with type 2 diabetes. Greater HbA1c reductions are noted with supervised exercise programs compared with unsupervised exercise programs (approximately 0.5–0.6% HbA1c reduction). Combined resistance and aerobic exercise programs offered greater reductions in HbA1c compared with individual aerobic or resistance training in isolation (approximately 0.2–0.6%) (SOR: **C**, meta-analysis of randomized controlled trials [RCTs] using disease-oriented outcome).

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A 2018 meta-analysis of 23 RCTs (N=1,605) compared different exercise training modalities for patients with type 2 diabetes mellitus (T2DM).[1] The patients (average age 55–72 years old) performed either combined aerobic and resistance training exercise, supervised aerobic exercise, supervised resistance training, unsupervised aerobic exercise, or no exercise. Interventions ranged from 2 to 9 months (most lasting 2–6 months) with varied duration for each exercise session and frequency of sessions. The primary endpoint was change in HbA1c levels before and after the exercise intervention. Compared with no exercise, combined exercise (3 trials, n=443, mean difference [MD] –0.53%; 95% CI, –0.68 to 0.45%), supervised aerobic exercise (11 trials, n=802, MD –0.30%; 95% CI, –0.60 to –0.45%), and supervised resistance training (5 trials, n=413, MD –0.30%; 95% CI, –0.38 to –0.15%) reduced HbA1c levels. Supervised aerobic exercise resulted in greater HbA1c reduction compared with unsupervised aerobic exercise and unsupervised resistance training (MD –0.60%; 95% CI, –0.83 to –0.30%; and MD –0.60%; 95% CI, –0.83 to –0.20%, respectively). Supervised resistance training also improved HbA1c more than unsupervised aerobic exercise and unsupervised resistance training (2 trials, n=135, MD –0.53%; 95% CI, –0.75 to 0.30%; 2 trials, n=48, MD –0.53%; 95% CI, –0.83 to –0.23%, respectively). However, supervised exercise did not result in significantly better HbA1c when the study duration was less than six months. Combined exercise resulted in the most significant reduction in HbA1c when compared with individual forms of exercise, supervised or unsupervised (supervised aerobic: MD –0.23%; 95% CI, –0.30 to –0.08%; unsupervised aerobic: MD –0.75%; 95% CI, –0.98 to –0.53%; supervised resistance training: MD –0.23%; 95% CI, –0.38 to –0.15%; unsupervised resistance training: MD –0.75%; 95% CI, –0.98 to 0.45%). No significant differences were noted between the other forms of exercise in effectiveness of HbA1c reduction. Limitations include variability of study period length, and exercise frequency and intensity.

A 2014 meta-analysis of 14 RCTs (N=915) compared aerobic exercise training, resistance training, and combined training on glycemic control for adult patients T2DM.[2] The trials included adults (mean ages 49–63 years old) with mean body mass indices of 27 to 44 kg/m^2. The primary endpoint was change in HbA1c levels obtained preintervention and postintervention. Exercise regimen duration ranged from 2 to 12 months and varied in frequency. When compared with resistance training, aerobic exercise resulted in a significant reduction in HbA1c (10 trials, n=515, MD –0.20%; 95% CI, –0.32 to –0.08). Combined training resulted in significant reductions in HbA1c when compared with aerobic exercise and resistance training, (9 trials, n=493, MD –0.17%; 95% CI, –0.31 to –0.03%; 5 trials, n=362, MD –0.62%; 95% CI, –0.95 to –0.30%, respectively). However, when studies at high risk for bias were excluded from analysis, only nonsignificant results were obtained. EBP

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Is there a difference in the incidence of surgical site infections in women who have planned versus unplanned cesarean delivery?

EVIDENCE-BASED ANSWER

Yes, an increased association of surgical site infections is noted in women who have undergone an emergency Cesarean delivery compared with those who had a planned Cesarean delivery (SOR: **A**, based on consistent retrospective cohort studies and a case-control study).

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A 2019 retrospective cohort study (N=219,859) assessed the risk of surgical site infections after cesarean delivery. Patients were women who had undergone a cesarean delivery within a publicly funded hospital in Ireland. Patients were mostly 25 years old or older (91%) with public insurance (69%). No exclusion criteria were reported. Surgical site infections were defined as infection affecting the wound or the uterus and occurring within 30 days of surgery. Emergency caesarian deliveries were associated with increased risk of surgical site infections compared with planned caesarian deliveries (risk ratio 1.1; 95% CI, 1.01–1.27). A key limitation of this study was the absence of body mass index data on the patients.

Another 2019 retrospective cohort study (N=453) assessed the risk of surgical site infections after cesarean delivery in severely obese pregnant women. Patients had a mean age of 30 years old with a singleton pregnancy and morbidly obese (body mass index >40 kg/m^2 before 20 weeks' gestation) from two different maternity hospitals in Scotland. They were largely Caucasian (80%) and nonsmoking (83%). A surgical site infection was defined as an infection occurring after a surgery and involving the skin, tissue, organs or implanted materials directly associated with the surgery. Emergency caesarian deliveries were associated with an increased risk of surgical site infections compared with planned caesarian deliveries (62 vs 41; adjusted odds ratio 1.64; 95% CI, 0.88–3.07) in severely obese women. This study was limited by the fact that no surgical site infections after hospital discharge were included.

A 2014 retrospective case-control observational study (N=158) assessed the risk of surgical site infections after cesarean delivery.[3] Surgical site infections were defined as maternal fever accompanied by spontaneous parting of the wound, a purulent discharge from the wound with or without positive bacterial culture, or local swelling or redness of the wound that resulted in wound reopening by the attending staff. Participants had a mean age of 26 years old, were mostly Caucasian (87.3%), and nonobese (73.4%) women from a single Brazilian hospital. Emergency caesarian deliveries were associated with increased risk of surgical site infections compared with planned caesarian deliveries (odd ratio 3.30; 95% CI, 1.63–6.67). This study was limited by the fact that no surgical site infections after hospital discharge were included. EBP

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Do appetite stimulants improve outcomes in frail older adults?

EVIDENCE-BASED ANSWER

Megestrol is weakly associated with weight gain in the frail older adult; however, megestrol is associated with increased risk of death and thromboembolic events (SOR: **B**, a meta-analysis with moderate heterogeneity and low-quality evidence). Mirtazapine is not recommended for use as an appetite stimulant (SOR: **C**, expert opinion).

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A 2012 meta-analysis (randomized controlled trial [RCT]=35; N=4,234) compared the effects of megestrol with placebo and other drugs in patients with anorexia-cachexia syndrome.[1] Included studies derived data from patients with comorbid conditions, including COPD, malignancy, acquired immunodeficiency syndrome, and cystic fibrosis. Data were collected independent of gender, age, or race with these demographic identifiers not reported in all trials. Age was only remarked on for 69 participants who were identified as elder, though all participants were adults 18 years old and above. Studies were excluded if patients had normal or increased body mass index. The studies included comparison of varied dosing regimens of megestrol (ranging from 100 to 1,600 mg daily), megestrol and nonspecific placebo, and megestrol and other drug classes (2.5–5 mg of dronabinol, 12 mg of cyproheptadine, and 3 mg of dexamethasone). Duration ranged 2 to 24 weeks, with primary outcome being weight gain. When megestrol is compared with the other appetite stimulants (not defined), an improvement in weight was noted (RCT=7; n=1,131; relative risk (RR) 1.66; 95% CI, 1.1–2.5; I^2=51%). Patients treated with megestrol versus placebo also saw an improvement in weight (RCT=10; n=1,106; RR 1.5; 95% CI 1.1–2.1; I^2=60%) and quality of life (RCT=3; N=381; RR 1.8; 95% CI, 1.1–2.9). However, patients treated with megestrol also saw an increase in death (RCT=11; n=1,367; RR 1.4; 95% CI, 1.04–1.9; I^2=0%) and thromboembolic events (RCT=12; n=1,604; RR 1.8; 95% CI, 1.1–3.2; I^2=0%). The quality of evidence for all the statistical analyses was rated as very low by the authors. This analysis contained limited demographic details and lacked isolated analysis of appetite stimulants other than megestrol.

In 2014, the American Geriatric Society recommended that mirtazapine should not be used for targeted appetite stimulation in frail older adults without other indication for the use of the medication (ie, depression).[2] The recommendation was constructed by a combination of targeted systematic review and expert opinion. This recommendation was given a SOR **C** (consensus guideline) by the authors. These guidelines also reinforced that inadequate evidence exists for efficacy and safety to provide recommendation on other appetite stimulants (mirtazapine, cannabinoids, thalidomide, anabolic steroids, and megestrol when used as an appetite stimulant). EBP

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Does screening asymptomatic adults for CVD using ECG improve health outcomes?

EVIDENCE-BASED ANSWER

Screening asymptomatic, high-risk diabetic adults with exercise electrocardiography (ECG) for cardiovascular disease (CVD)-related events does not improve patient outcomes (SOR: **A**, systematic review of randomized control trials [RCTs]). Screening adults with resting ECG for CVD-related events also does not improve patient outcomes based on a variety of measures (SOR: **C**, systematic review of nine fair-quality cohort studies). Insufficient evidence exists to support screening moderate-to-high-risk adults for CVD (SOR: **C**, expert opinion).

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A 2018 systematic review of two RCTs and 14 cohort studies (N=77,140) evaluated the utility of adding screening ECG to traditional factors in assessing risk for cardiovascular outcomes.[1] The two RCTs (N=1,151) examined exercise ECG testing, with five cohorts (N=9,582) also examining exercise ECG and the remaining nine cohorts (N=68,475) measuring resting ECG testing. Patients ranged in age from 50 to 75 years old and were from the United States, Western Europe, and Japan. The two RCTs followed high-risk, asymptomatic diabetic patients (mean hemoglobin A1c 7.7%–8.6%) for up to 3.6 years. Of that group, 34% were female, 27% were smokers, and 74% had hypertension. One RCT (n=631) used bicycle exercise testing or single-photon emission computed tomography and found no significant difference in all-cause mortality, nonfatal myocardial infarction (MI), nonfatal stroke or heart failure requiring hospitalization or emergency services compared with the control group (hazard ratio [HR] 1.0; 95% CI, 0.59–1.7). The other RCT (n=520) used exercise treadmill testing and found no significant difference in nonfatal MI or cardiac death compared with those not screened (HR 0.85; 95% CI, 0.39–1.8). One exercise ECG cohort study (n=988) measured effectiveness of screening to help reclassify patients as high risk or low risk for cardiac events by the area under curve (AUC) where 16.5% had atypical chest pain and the rest were reported as asymptomatic. The initial risk as estimated by the Framingham Risk Score (FRS) was low for 16.9%, intermediate for 69.2%, and high for 13.9%. The AUC modeling estimates the proportion of patients that are successfully classified for risk of cardiac events by adding in measurable variables. Adding in exercise ECG results to a slightly modified FRS model did not significantly help reclassify patients of high or low risk (AUC improvement 0.02, $P=.3$). All other exercise ECG cohorts had follow-up ranging from 6 to 8 years, and none showed significant findings of improvement. The included resting ECG cohort studies did not include significant indicators such as *P*-values or confidence limits, were variable in cardiovascular disease (CVD) assessment tools, and used different risk categories.

Based largely on the above review, in 2018, the U.S. Preventive Services Task Force confirmed its previous recommendations regarding ECG screening for CVD in asymptomatic adults.[2] Screening with resting or exercise ECG in low-risk asymptomatic adults as defined by a less than 10% 10-year risk of CVD using either the Framingham Risk Score or the Pooled Cohort Equations was not recommended (D statement; moderate to high certainty). At the time of the review, insufficient evidence existed to assess screening with resting or exercise ECG in asymptomatic adults with intermediate or high risk of CVD events (I statement; evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined). EBP

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Do children with egg allergy ever outgrow that allergy?

EVIDENCE-BASED ANSWER

Yes. About half of children will outgrow egg allergy by age two years old, and about 50% to 70% by age six years old. (SOR: **B**, consistent prospective cohort studies). Certain factors are associated with persistence of egg allergy, including severity of allergic reaction, intolerance to baked egg, and gastrointestinal manifestation of allergy (SOR: **B**, prospective cohort studies).

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A retrospective cohort study in Turkey investigated factors associated with persistence of egg allergy in 203 children.[1] Children with confirmed egg allergy were followed every 4 to 8 months until age six years old, and oral food challenges were performed in children who had no anaphylaxis to egg in the last year. Egg allergy resolved in 71% (n=145) of children by age six years old, determined by a negative food challenge test. Factors associated with persistence of allergy compared with resolution of allergy included egg serum IgE levels >6.2 Ku/L (hazard ratio of developing tolerance [HR], 0.25; 95% CI, 0.16–0.39), anaphylaxis caused by egg (HR, 0.31; 95% CI, 0.18–0.52), gastrointestinal symptoms (HR, 0.59; 95% CI, 0.35–0.98), and cow's milk allergy (HR, 0.69; 95% CI, 0.49–0.97).

A prospective cohort study in Australia evaluated 140 children with egg allergy at one and two years old for allergy resolution.[2] Patients were initially identified by skin prick test to egg whites and then confirmed with oral food challenge and egg white, IgE levels, or with a previous objective immediate reaction to eggs. Resolution was defined as passing an oral food challenge or parental report of tolerance. Egg allergy resolved in 47% of infants by two years (95% CI, 37–56%). Children who were tolerant to baked egg at one year were five times more likely to have allergy resolution at two years, compared with those who were baked egg allergic at one year (odds ratio [OR], 5.3; 95% CI, 1.4–21). Additionally, the children who were tolerant to baked egg at one year and consumed baked egg frequently (>5 times per month vs no consumption) were three times more likely to have tolerance to raw egg (OR, 3.5; 95% CI, 1.4–9.0).

A 2014 observational study evaluated the natural history and clinical predictors of egg allergies in a cohort of 512 infants enrolled at 3 to 15 months old at five sites, which included a subset of 213 egg allergic children.[3] Enrollment criteria for the whole cohort included atopic children with likely egg or milk allergy at risk to develop peanut allergy but without current peanut allergy. Patients were included if they had a history of immediate allergic reaction to eggs and a positive skin prick test. The specific egg allergic cohort of 213 children were evaluated in person at enrollment, six, 12 months and yearly thereafter, with additional telephone follow-up between each visit and open to receive calls about new allergic reactions. Resolution was established by successful oral food challenge of eggs, which was run if IgE serum was less than 2 kU_A/L. Egg allergy resolved in 105 of the egg allergy cohort (49%), at a median age of 72 months. Of those with unresolved allergy, 38% reported tolerating at least some baked egg products. EBP

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Does an elevated serum eosinophil level predict a positive response to inhaled corticosteroids in patients with chronic COPD?

EVIDENCE-BASED ANSWER

Possibly. Patients with an elevated blood eosinophil level, particularly those with an absolute count of 300 cells per microliter or more, may have 20% to 40% fewer COPD exacerbations after starting inhaled corticosteroids (ICS) (SOR: **B**, systematic review of post hoc analyses of randomized controlled trials and observational trials with inconsistent results). The Global Initiative for Chronic Lung Disease recommends using a peripheral blood level of greater than 300 eosinophils per microliter combined with a clinical assessment of exacerbation risk to identify patients who are likely to benefit from ICS (SOR: **C**, expert opinion).

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A 2020 systematic review of 11 post hoc analyses of 13 randomized controlled trials (RCTs; N=25,881) and five observational studies (N=109,704) assessed the predictive value of blood eosinophil counts to determine which patients with COPD would likely benefit from using inhaled corticosteroids (ICS) to prevent exacerbations.[1] The review evaluated ICS versus non-ICS response at three blood eosinophil thresholds: 2% (relative to total white blood cell count), 150, and 300 cells per microliter. The interventions included ICS monotherapy, ICS plus a long-acting beta-agonist (LABA), and ICS plus LABA plus a long-acting muscarinic agonist (LAMA); eight of the post hoc analyses (N=20,929) used fluticasone, two (N=3,685) used beclomethasone, and one (N=1,267) used budesonide. Comparators were placebo, LABA (without ICS), and LABA plus LAMA (without ICS). Of the 13 RCTs, 10 had balanced treatment arms, where the only difference between intervention and control groups was the addition of an ICS in the intervention group. However, three studies used different baseline intervention and control medications that resulted in an inability to completely isolate the effect of adding an ICS to the intervention group. Measured outcomes included the risk of moderate or severe COPD exacerbations, defined as symptoms requiring antibiotic and/or steroid administration or hospital admission. In studies where the effect of ICS could be isolated, an eosinophil cutoff of 300 eosinophils per microliter was the most helpful in predicting who would benefit from ICS (see **TABLE**). In pooled analyses that included studies where the effect of ICS could not be isolated, an eosinophil cutoff of 2% helped predict who would benefit from ICS. A threshold of 150 cells per microliter was only moderately helpful in determining response to ICS. Of the five observational studies, one (N=24,732) found a significant association between blood eosinophil counts and the impact of ICS

TABLE. Effect of inhaled corticosteroid on the risk of experiencing a moderate or severe COPD exacerbation, stratified by blood eosinophil count

No. of studies	No. of patients	ICS effect isolated[a]	Eosinophil count threshold	RR (95% CI) of COPD exacerbation[b]
9	18,393	Mixed	≥2%	**0.84 (0.75–0.93)**
			<2%	0.95 (0.88–1.02)
7	11,622	Yes	≥2%	**0.80 (0.74–0.85)**
			<2%	**0.89 (0.81–0.97)**
4	12,961	Yes	≥150 cells/μL	**0.65 (0.52–0.79)**
			<150 cells/μL	**0.87 (0.79–0.95)**
3	6,696	Mixed	≥300 cells/μL	0.76 (0.43–1.09)
			<300 cells/μL	NR
2	3,347	Yes	≥300 cells/μL	**0.61 (0.44–0.78)**
			<300 cells/μL	0.98 (0.82–1.14)

Data from a systematic review of post-hoc analyses of RCTs.[1] [a] Most of the post hoc analyses had balanced treatment arms, where the only difference between interventions and controls was the addition of an ICS in the intervention group (ie, ICS effect isolated=yes); however, three studies used different baseline intervention and control medications that resulted in an inability to completely isolate the effect of adding an ICS to the intervention group (ie, ICS effect isolated=mixed). [b] Relative risk <1 favors ICS; statistically significant results in bold font. ICS=inhaled corticosteroid; NR=not reported; RR=relative risk.

on COPD exacerbation frequency, noting a 24% (95% CI, 15–33%) relative risk reduction in those treated with ICS who had eosinophil counts of 300 or more cells per microliter compared with those whose counts were below 300 cells per microliter. However, the four other observational trials failed to show an association between blood eosinophil counts and ICS impact on exacerbations. The review was limited by the lack of information on patient age, gender mix, and COPD severity. Furthermore, the individual trials were deemed to be of low to very low quality, largely because of risk of bias as a result of unclear blinding of outcome assessment, incomplete outcome data, and selective reporting of results.

A 2020 consensus-based guideline from the Global Initiative for Chronic Obstructive Lung Disease recommended measuring the blood eosinophil count in patients with COPD to help predict the ability of ICS to prevent exacerbations, noting that those with an eosinophil count greater than 300 cells per microliter were most likely to benefit from ICS (strong support for ICS based on prespecified, post hoc, and other analyses of drug trials).[2] Conversely, the guideline noted that patients with a blood eosinophil level below 100 cells per microliter were unlikely to be helped by ICS (strong recommendation against ICS based on multiple drug trials). The guideline recommended that the blood eosinophil count should always be combined with a clinical assessment of COPD exacerbation risk (eg, based on prior severity and frequency of exacerbations) when considering initiating ICS treatment (strong support based on prespecified, post hoc, and other analyses of drug trials). EBP

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Does azithromycin increase likelihood of potentially lethal dysrhythmia?

EVIDENCE-BASED ANSWER

No. Azithromycin is not associated with an increased risk of arrhythmias, cardiac disorders, or mortality (SOR **A**: systematic reviews of randomized controlled trials, cohort trials, and case-control studies).

DOI 10.1097/EBP.0000000000001197

A 2019 systematic review and meta-analysis identified seven placebo-controlled randomized trials reporting on 115 adverse cardiac events in 1,715 patients taking macrolide antibiotics.[1] The patients had an average age ranging from 55 to 73 years old, and they were evaluated in secondary care settings. The indication for macrolide antibiotics included treatment or prevention of COPD exacerbations, secondary prevention of acute coronary syndrome or abdominal aortic aneurism expansion, treatment of postoperative ileus, and prevention of bronchiolitis obliterans syndrome after lung transplantation. Most studies used PO azithromycin at doses of 250 to 750 mg, given daily to weekly, for up to one year. Two studies used macrolides other than azithromycin (total N=242). The adverse cardiac outcomes included arrhythmias, acute coronary syndrome, and unspecified events. No difference was observed in rates of adverse cardiac outcomes between macrolides and placebo (odds ratio [OR], 0.87; 95% CI, 0.54–1.4). The review also reported all-cause mortality by subgroup analysis of type of macrolide and found no difference in rate between azithromycin use and placebo (N=204,719; OR, 0.97, 95% CI, 0.85–1.1). Although the heterogeneity of the seven studies was minimal (I^2=9.06%), the review was limited by the inability to test the effect of different doses and decipher if the outcome was an adverse event or a sequelae of the disease process.

A 2018 systematic review and meta-analysis of 33 studies (13 randomized controlled trials [RCTs], 15 cohort, and 5 case-control; N=22,601,032) evaluated the cardiac

safety of macrolide antibiotics.[2] In 19 studies information was found in medical or health insurance databases. The review excluded studies involving patients with HIV, sepsis, and those in intensive care unit settings. The patients had an average age between 40 and 86.5 years old; they were taking macrolide antibiotics for various reasons including upper or lower respiratory infections and complications from coronary artery disease. Of the 33 studies, 17 included patients taking azithromycin, 14 had patients on other macrolide antibiotics, and two did not specify the macrolide used. Azithromycin dose was reported in nine of the trials and varied between 250 and 600 mg, given daily for 3 to 14 days or weekly for up to three months. The comparator was placebo or no antibiotics in 15 studies, whereas a nonmacrolide antibiotic was prescribed in 17 trials and one study did not specify the control medication. Nine studies (one RCT, six cohort, two case-control studies; N=5,502,206) found that the risk of short-term arrhythmia was not associated with macrolide versus nonmacrolide exposure (OR, 1.2; 95% CI, 0.91–1.6). Similarly, thirty-day cardiovascular mortality was no greater with macrolide use when compared with placebo or nonmacrolide use (1 RCT, 6 cohort, 2 case-control studies, N=18,288,848; OR, 1.2; 95% CI, 0.94–1.6). Limitations included considerable heterogeneity (I^2>75%) as a result of different macrolide antibiotic types, doses, and indications, as well as various comorbidities and ages of the patients. Also, there was potentially missing data in the medical and health insurance databases used by the majority of the studies. EBP

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Does CBT decrease physical symptoms in somatic symptom disorder in adults?

EVIDENCE-BASED ANSWER

Yes. In adults with somatic symptom disorder, cognitive behavioral therapy (CBT) compared with standard care leads to a small decrease in physical symptoms for up to one year after therapy (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Comparing pre- and posttreatment, CBT is effective in both group and individual sessions, with treatment ≥12 weeks and sessions lasting ≥50 minutes (SOR: **B**; meta-analysis of RCTs).

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A 2014 meta-analysis of 21 RCTs evaluated the effectiveness of psychological therapies for patients (N=2,658) diagnosed with somatoform disorders and medically unexplained physical symptoms (MUPS).[1] Patients were adults (76% women; mean ages ranging from 35 to 49 years) who met the diagnosis for somatoform disorder (based on Diagnostic and Statistical Manual of Mental Disorders [DSM], DSM-IV-Text Revision [TR], International Classification of Diseases [ICD]-9, or ICD-10 codes or criteria) or a diagnosis of MUPS. Psychological therapies included cognitive behavioral therapy (CBT), behavioral therapy, third-wave CBT, integrative therapy, and psychodynamic therapy. CBT was compared with standard care/waitlist, enhanced/structured care (adjunctive counseling, patient education, or reattribution training), and behavioral therapy with a primary end point of somatic symptom severity. Patients used a self-reported scale where they rated their physical symptom severity with outcomes measured immediately, after 12 months of treatment, and in the 12-month period following treatment. CBT varied in the number of sessions from 1 to 10 times and with duration ranging up to six months. At the end of treatment, the CBT group compared with standard care/waitlist showed a small decrease in physical symptoms (6 studies, n=593; standard mean difference [SMD], –0.37; 95% CI, –0.69

to –0.05; I^2=70%). At one-year follow-up, CBT showed a small decrease in physical symptoms in comparison to standard care (4 studies, n=496; SMD, –0.29; 95% CI, –0.49 to –0.09; I^2=17%). Only two studies evaluated one-year follow-up and found that CBT moderately decreased long-term severity of symptoms compared with standard care (2 studies, n=228; SMD, –0.57; 95% CI, –0.8 to –0.24; I^2=0%). A limitation of the analysis was that standard care varied considerably between studies.

A 2019 meta-analysis (15 RCTs, N=1,671) compared treatment of somatoform disorders and MUPS with CBT versus usual care, enhanced care, or waiting list by comparing patient's reduction in physical symptoms.[2] There were 13 trials that overlapped with the above meta-analysis. Patients included adults, mean ages ranging from 34 to 49 years, with somatic symptom disorder, MUPS, somatization, somatoform disorder, or functional somatic symptom by DSM-III, DSM-IV, DSM-IV-TR, DSM-5 or *ICD-10* codes or criteria. Interventions included CBT versus usual care, enhanced, or waitlist care. Several different scales were used to rank patient's symptom severity with higher values indicating increased severity. Data were pooled using the generic inverse variance method and were expressed as mean differences (MDs). The mean difference is the difference between the symptom severity mean in the pretreatment group compared with symptom severity posttreatment, with higher negative mean differences representing more significant decrease in symptom severity. Primary outcomes followed pre to posttreatment severity of somatic symptoms. For patients receiving CBT, physical symptoms were reduced pre to posttreatment (10 studies, n=1,148; MD, –1.3; 95% CI, –2.2 to –0.39; I^2=86%). CBT pre -to posttreatment reduced somatic symptoms within group and individual setting (4 studies, n=539; MD, –4.4; 95% CI, –8.5 to –0.39 and 6 studies, n=657; MD, –1.00; 95% CI, –1.9 to –0.1). Comparing somatic symptoms pre and posttreatment, CBT was effective when treatment was ≥12 weeks duration but no different with <12 weeks duration (7 studies, n=781; MD, –2.3; 95% CI, –4.1 to –0.52 and 3 studies, n=415; MD, –0.41; 95% CI, –1.4 to 0.61). Pre and posttreatment scores showed that somatic symptoms were reduced if the sessions were ≥50 min but did not change with sessions <50 minutes (8 studies, n=978; MD, –1.5; 95% CI, –2.5 to –0.47 and 2 studies, n=218; MD, –0.33; 95% CI, –2.4 to 1.7). Limitations of this study included the high heterogeneity of the primary meta-analysis and lack of blinding. EBP

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Do alpha-blockers increase the passage of ureteral stones 1 cm or smaller compared with standard therapy?

EVIDENCE-BASED ANSWER

Alpha-blocker therapy improves rate of clearance (116–267 more per 1,000 patients) and decreases time to stone passage by three or more days compared with no treatment or standard therapy, independent of stone location. This effect is greatest with ureteral stones greater than five mm. Hospitalization rates are reduced (1.06 fewer per 1,000 patients) and the risk of adverse events does not increase (SOR: **B**, meta-analyses of consistent but moderate-to low-quality, randomized controlled trials).

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A 2018 meta-analysis of 67 randomized controlled trials (RCTs; N=10,509) assessed efficacy of alpha-blockers on ureteral stone expulsion rate and time to stone clearance.[1] Adults (mean ages, 32–56 years old)

with acute ureteric colic and a single ureteral calculus less than one cm confirmed by imaging were given alpha-blocker monotherapy, placebo, or standard therapy. Standard therapy included hydration therapy and fluid management, NSAIDs, anticholinergic agents, antispasmodics, and corticosteroids. Alpha-blocker therapy included primarily tamsulosin (0.2 or 0.4 mg daily) and alfuzosin (10 mg daily). Stone clearance (determined by imaging, resolution of symptoms or passage of stone) and major adverse events were the primary outcomes evaluated at the end of the study (10–28 days). Time to stone expulsion, hospitalizations, pain episodes, diclofenac use, and surgical intervention were evaluated as secondary outcomes. Alpha-blocker use increased successful stone clearance compared with standard therapy (risk ratio [RR], 1.4; 95% CI, 1.4–1.6). This effect was strongest for distal stones larger than five mm in diameter (10 trials; n=2,887; RR, 1.5; 95% CI, 1.2–1.7) compared with stones less than five mm (14 trials; n=2,622; RR, 1.1; 95% CI, 0.98–1.2). Expulsion time was reduced with alpha-blocker therapy (37 trials, n=6,031, mean difference [MD], –3.4 days; 95% CI, –4.2 to –2.6). Tamsulosin reduced hospitalization risk compared with placebo or standard therapy (11 trials; n=1,606; RR, 0.6; 95% CI, 0.4–0.9). No significant difference in the risk of adverse events occurred between the groups (18 trials; n=3,324; RR, 1.2; 95% CI, 0.8–2). Limitations included lack of high-quality trials available for analysis, inconsistent reporting of adverse events, and not all trials used radiologic imaging to verify stone expulsion.

A 2016 meta-analysis of 55 RCTs (including many in the above meta-analysis, N=5,990) examined the efficacy of alpha-blockers in the treatment of ureteric stones.[2] Adult patients (mean age, 40 years) received alpha-blocker monotherapy (similar agents as above), placebo, or no added therapy to facilitate stone passage. Mean stone size was 5.7 mm for the treatment and control groups (41 studies). Upper and middle ureter stones were evaluated in 11 studies, whereas the remaining evaluated lower ureter stones. The primary outcome was the proportion of individuals who passed the ureter stone. Secondary outcomes included the time to pass the ureteral stone, pain episodes, surgical interventions, hospitalizations, and serious adverse events. Duration of follow-up ranged from 7 to 42 days, with a mean of 28 days. Stone expulsion was evaluated via radiographic imaging or by the absence of needing further intervention. Patients receiving alpha-blockers for 28 days or less had a higher likelihood of stone passage regardless of stone location (RR, 1.5; 95% CI, 1.4–1.6; number needed to treat=4). For every one-mm increase in stone size, the likelihood risk ratio for stone passage increased by 9.8% (2.5–18%; $P<.01$). Compared with controls, alpha-blocker therapy resulted in decreased passage time (24 trials; n=2,862; MD, –3.8 days; 95% CI, –4.5 to –3.1), pain episodes (13 trials, n=1,235; –0.74 episodes; 95% CI, –1.3 to –0.21), and hospitalizations (8 trials; n=1,007; RR, 0.37; 95% CI, 0.22–0.64). The rate of adverse effects between groups was similar (RR, 1.5; 95% CI, 0.24–9.4). Limitations included lack of consistent verification of stone expulsion by radiographic imaging, type of alpha-blocker therapy administered, variable follow-up periods, and clinical heterogeneity among studies. EBP

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Does vitamin D deficiency in pregnancy increase the risk of postpartum depression?

EVIDENCE-BASED ANSWER

Perhaps. Low serum 25-hydroxyvitamin D levels in pregnancy may increase the odds of developing postpartum depression (PPD) and symptoms of PPD (SOR: **C**, mixed evidence from two systematic reviews of randomized controlled trials, cohorts, and case-control studies).

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A 2019 systematic review (N=3,896) of six cohort studies and one case-control study investigated

the association between vitamin D deficiency during pregnancy and postpartum depression (PPD).[1] Pregnant women had 25-hydroxyvitamin D (25(OH)D) levels checked at various points in their pregnancy or within 24 hours of childbirth, and PPD symptoms were assessed using the Edinburgh Postpartum Depression Scale (EPDS), a 10-question depression screening tool. One cohort (n=1,040) of Australian women collected infants' cord blood immediately after delivery to measure if the cord blood was above or below a 25(OH)D level of 25 ng/mL. Mothers with children whose cord blood was in the lower group experienced a significantly greater proportion of maternal depressive symptoms compared with those in the higher group of 25(OH)D levels (adjusted risk ratio [aRR], 0.35; 95% CI, 0.17–0.69). However, this relationship was not maintained at six months postpartum. Another cohort study of 213 Chinese women examined the relationship of vitamin D levels taken 24 to 48 hours postpartum and a subsequent diagnosis of PPD. Women with 25(OH)D levels below 10.2 ng/mL were significantly more likely to be diagnosed with PPD compared with those above that level (odds ratio [OR], 7.2; 95% CI, 3.8–13). A cohort study (n=796) assessed the differences in PPD symptoms reported in Australian women three days postpartum and their vitamin D levels. Women with vitamin D levels in the lowest quartile (<47 nmol/L) self-reported more PPD symptoms than those in the highest quartile (>70 nmol/L) of vitamin D levels (adjusted OR [aOR], 2.2; 95% CI, 1.3–3.8). No difference was observed in the final case-control study (n=1,480) for Danish women at 24 to 25 weeks of gestation for vitamin D levels of PPD.

A 2018 systematic review (N=4,351) of four prospective cohorts, one cross-sectional, one case-control, two secondary analysis studies, and one randomized controlled trial (RCT) assessed the relationship between serum 25(OH)D levels during pregnancy and subsequent incidence of PPD.[2] Women had antenatal serum 25(OH)D levels checked from nine to 36 weeks of gestation and subsequently from birth to one year postpartum. PPD symptoms were most commonly assessed with the EPDS or a unique questionnaire using questions from the EPDS. The RCT randomized 153 Iranian women to 2,000 IU vitamin D supplementation daily versus placebo from 26 weeks of gestation until delivery. Serum 25(OH)D levels were checked at 38 to 40 weeks of gestation, four weeks postpartum, and eight weeks postpartum. Women receiving vitamin D supplementation were more likely to be in the lower EPDS group (<9 points) compared with the control group at four (91% vs 60%; $P<.001$) and eight weeks postpartum (89% vs 64%; $P<.001$). One secondary analysis of an RCT (n=1,040) obtained cord blood samples from infants from Australian mothers and compared vitamin D levels and PPD symptoms in mothers. There was no significant difference in mothers with lower vitamin D levels compared with mothers with higher levels for PPD at six weeks postpartum (aRR, 0.92; 95% CI, 0.84–1.02) or six months postpartum (aRR, 0.96; 95% CI, 0.88–1.1). Another secondary analysis of an RCT (N=126) of American women noted an association between lower vitamin D levels in pregnancy and higher depressive symptom scores but did not find an increase in overt depressive disorders, including PPD. Three of the prospective design studies found an association between higher vitamin D levels and decreased odds of PPD, including a study of 248 Chinese women, which showed a higher levels of vitamin D was associated with decreased odds of PPD three months postpartum (aOR, 0.81; 95% CI, 0.70–0.91). The other prospective study and case-control study did not find any association between serum 25(OH)D and PPD). EBP

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How effective is progestin-only emergency contraception in obese women?

EVIDENCE-BASED ANSWER

Levonorgestrel (LNG) and ulipristal acetate (UPA) for emergency contraception are less effective in obese women than in normal weight women (SOR **A**, meta-analyses of randomized controlled trials [RCTs]). LNG is less effective than UPA (SOR A; meta-analysis of RCTs).

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A 2017 meta-analysis of four RCTs estimated the effect of increased body weight on pregnancy rates from 6,873 women taking levonorgestrel (LNG) for emergency contraception.[1] The average age was 27 years, and the mean weight was 59 kg. Of the total patients, 79% had a body mass index (BMI) of ≤25 kg/m^2 (normal), 17% had a BMI of 25 to 30 kg/m^2 (overweight), and 4.3% had a BMI of ≥30 kg/m^2 (obese). Patients took LNG as a single 1.5-mg dose or as 0.75 mg given 12 hours apart up to 120 hours after unprotected intercourse. The outcome was defined as a positive pregnancy test one week after a missed period confirmed by ultrasound. The overall pregnancy rate was low at 1.2%. Pregnancy rates were higher in obese women compared with normal weight women (odds ratio [OR], 8.3; 95% CI, 2.7–25). There was no difference in pregnancy rates between overweight women compared with normal weight women (OR, 0.96; 95% CI, 0.42–2.2). No adverse effects were reported. This result may not be generalizable because three out of the four RCTs did not report any pregnancies in the obese women. In addition to BMI, timing of when LNG is taken in relation to sexual intercourse and day of ovulation affects efficacy. All the obese women who became pregnant took the emergency contraceptive pill after their expected date of ovulation.

A 2011 meta-analysis of two RCTs (N=3,445) assessed the effectiveness of emergency contraceptive pills (ECPs) in women after unprotected intercourse using a nominal logistic model.[2] Patients had a mean age of 25 years and had taken emergency contraception 0 to 120 hours after unprotected intercourse. Patients had regular menstrual cycles and were not on a hormonal birth control method. Patients with an intrauterine device, history of sterilization, actively breast feeding, or younger than 16 years were excluded. Patients received LNG 1.5 mg orally versus ulipristal acetate (UPA) 30 mg marketed formulation or 50 mg nonmicronized formulation orally. The primary outcome was to determine if BMI and weight along with other covariates increased the probability of becoming pregnant after emergency contraceptive use. Obese (BMI, ≥30 kg/m^2) and overweight (BMI, 25–29 kg/m^2) women each had a higher risk of pregnancy compared with normal/underweight women (BMI, <25 kg/m^2) when using ECPs (OR, 3.6; 95% CI, 2–6.5 and OR, 1.5; 95% CI, 0.75–3). Obese women who took LNG had the greatest risk of pregnancy compared with normal/underweight women (OR, 4.4; 95% CI, 2.1–9.4). Overweight women who took LNG also had a greater risk of pregnancy compared with normal/underweight women (OR, 2.1; 95% CI, 0.86–4.9). Obese women who took UPA had a greater risk of pregnancy compared with normal/underweight women (2.6%; 95% CI, 0.89–7). There was no difference for overweight women who took UPA compared with normal/underweight women (OR, 0.97; 95% CI, 0.27–2.8). Overall, the risk of pregnancy was reduced by almost 50% among women using UPA versus LNG (OR, 0.55; 95% CI, 0.32–0.93). The major limitations of this study were the small number of women with an obese BMI and a small number of total pregnancies in the overweight and obese women. EBP

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Are DOACs effective in patients with BMI >35?

EVIDENCE-BASED ANSWER

Yes. Treatment of venous thromboembolism (VTE) or atrial fibrillation in patients with elevated BMIs with a direct oral anticoagulant (DOAC) appears to be equivalent to warfarin in the prevention of recurrent VTE or stroke. There is no difference in major bleeding events for obese patients treated with DOACs compared with warfarin therapy (SOR: **B**, consistent observational studies).

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A 2020 meta-analysis of four observational cohort studies and one ad hoc analysis of randomized controlled trial findings (N=8,742) evaluated the rate of stroke or systemic embolization and major bleed in adults on direct oral anticoagulant (DOAC) treatment (apixaban or rivaroxaban) compared with standard warfarin therapy.[1] Patients had nonvalvular atrial fibrillation and a body mass index (BMI) of >40 kg/m^2 (or weight >120 kg). Over the follow-up period of 10 to 20 months, there was no statistically significant difference in stroke or systemic embolization rate between the DOAC and warfarin treatment groups (odds ratio [OR], 0.85; 95% CI, 0.6–1.2). There were fewer major bleeding events in the DOAC treatment group (OR, 0.63; 95% CI, 0.43–0.94); however, this relationship did not remain in subgroup analysis of individual drugs apixaban (three trials; N=602; OR, 0.59, 95% CI, 0.33–1.1) or rivaroxaban (3 trials; N=3,762; OR, 0.61; 95% CI, 0.35–1.1).

A 2020 meta-analysis of five observational retrospective cohort studies (N=6,585), compared rates of recurrent venous thromboembolism (VTE) and major bleeding events in obese patients (BMI >40 kg/m^2, weight >120 kg) with VTE treated with a DOAC (apixaban or rivaroxaban) or warfarin.[2] No statistically significant difference was observed in the rate of recurrent VTE after six months in patients in either treatment group (OR, 1.1; 95% CI, 0.93–1.2). No statistically significant difference was observed in risk of major bleeding events for those treated with a DOAC compared with warfarin (OR, 0.80; 95% CI, 0.54–1.2).

A 2020 retrospective matched cohort study (N=1,840) evaluated the safety and efficacy of DOACs versus warfarin for the treatment of acute VTE among hospitalized adult patients weighing between 100 and 300 kg.[3] Of the patients who received a DOAC (apixaban, dabigatran or rivaroxaban), no difference was seen in VTE recurrence among patients receiving a DOAC versus warfarin (6.5% vs 6.4%; hazard ratio, 1.0; 95% CI, 0.71–1.5) during the 12-month study period. Additionally, no statistically significant difference exists in rates of bleeding in patients receiving a DOAC compared with those receiving warfarin (1.7% vs 1.2%; P=.31). EBP

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In patients with type 2 diabetes, which GLP-1 receptor agonist results in the greatest weight reduction?

EVIDENCE-BASED ANSWER

All glucagon-like peptide 1 receptor agonists except albiglutide are associated with more weight loss than placebo, although the weight loss is modest (0.78–3.8 kg) and may not be clinically meaningful (SOR: **C**, meta-analysis of randomized controlled trials [RCTs] and 2 RCTs). When compared with each other, liraglutide (–1.2 kg) and twice daily exenatide (–0.9 kg) resulted in greater weight loss than lixisenatide (SOR: **C**, meta-analysis of RCTs and 2 RCTs). Semaglutide, both oral and injectable, produced the greatest weight loss in type-2 diabetes mellitus patients compared with placebo and liraglutide (SOR: **B**, RCTs.)

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A 2016 systematic review of 34 RCTs (N=14,464) assessed the safety and efficacy of glucagon-like peptide 1 (GLP-1) receptor agonists in the treatment of type 2 diabetes.[1] The mean age was 56 years, mean HbA1c was 8.2%, mean duration of diabetes mellitus (DM) was 8.1 years, and 50% were women. Baseline weights were not reported. Patients were on metformin, sulfonylureas, thiazolidinedione, insulin alone, or any combination of these. All clinical trials lasted 24 to 32 weeks and compared GLP-1 receptor agonists (albiglutide 50 mg weekly, dulaglutide 1.5 mg weekly, exenatide 10 mcg twice daily and exenatide 2 mg weekly, liraglutide 1.8 mg daily, and lixisenatide 20 mcg daily) to placebo or to another GLP-1 receptor agonist. Primary outcomes were cardiometabolic effects (weight, heart rate, blood pressure, and lipids), and weight loss was a secondary outcome. Changes in body weight were reported in 14,054 patients. All GLP-1 receptor agonists resulted in more weight loss than to placebo, with the exception of albiglutide (see **TABLE**). When compared with each other, liraglutide and twice daily exenatide resulted in a significantly greater weight loss than lixisenatide (mean difference [MD], –1.17 kg; 95% CI, 0.19–2.15 kg and MD, 0.89 kg; 95% CI, 0.01–1.76 kg). All GLP-1 receptor agonists compared with placebo had higher rates of hypoglycemia (except albiglutide), nausea (except albiglutide), vomiting, and diarrhea (except for lixisenatide). Comparing GLP-1s to each other, there was no difference in the rates of hypoglycemia. Once weekly exanatide had significantly lower risk of nausea compared with twice daily exanatide and dulaglutide (odds ratio [OR], 0.42; 95% CI, 0.28–0.64 and OR, 0.34; 95% CI, 0.18–0.65). Liraglutide and lixisenatide both had higher rates of nausea compared with once weekly exanatide (OR, 2.6; 95% CI, 1.6–4.4 and OR, 2.2; 95% CI, 1.2–3.9).

A 2019 RCT compared the efficacy of oral semaglutide 14 mg daily, injectable liraglutide 1.8 mg daily, or placebo in adults with type-2 diabetes (n=711).[3] Patients were on average 56 years with a mean HbA1c of 8%, duration of DM of 7.6 years, 48% women, and mean body mass index (BMI) of 33 kg/m^2. Semaglutide and liraglutide were titrated up to the doses over eight and two weeks, respectively, for a 52-week period.

TABLE. Weight loss associated with GPL-1 receptor agonists compared with placebo in adults with type-2 diabetes

GLP-1 agent	# RCTs	n	Treatment duration (wk)	Weight loss in kg (95% CI)
Albiglutide 50 mg weekly[1]	1	400	24 to 30	–0.41 (–2.32 to 1.5)
Dulaglutide 1.5 mg weekly[1]	4	1,087	24 to 26	–1.6 (–2.5 to –0.66)
Exenatide 10 mcg twice daily[1]	13	2,580	24 to 30	–1.7 (–2.3 to –1.1)
Exenatide 2 mg weekly[1]	4	1,087	24 to 30	–1.5 (–2.6 to –0.4)
Liraglutide 1.8 mg daily[1]	9	2,324	24 to 26	–2 (–2.7 to –1.3)
Lixisenatide 20 mcg daily[1]	7	2,238	24	–0.78 (–1.5 to –0.09)
Semaglutide 0.5 mg weekly[3]	1	257	30	–2.8 (–3.9 to –1.6)
Semaglutide 1 mg weekly[3]	1	259	30	–3.6 (–4.7 to –2.4)
Semaglutide 14 mg tablet daily[2]	1	306	52	–3.8 (–4.8 to –2.7)

GLP-1 = glucagon-like peptide 1; RCT = randomized controlled trial.

Patients could stay on metformin, a sodium-glucose cotransporter-2, and less than two weeks of insulin. The primary outcome was HbA1c reduction and secondary outcomes included weight loss. Oral semaglutide had superior weight loss versus placebo and injectable liraglutide at 52 weeks (TABLE and estimated treatment difference, –1.8 kg; 95% CI, –2.6 to –1.0 kg). Overall, 45% of semaglutide patients compared with 25% of liraglutide patients achieved a 5% body weight reduction at 52 weeks (estimated odds ratio, 2.4; 95% CI, 1.7–3.4). Gastrointestinal side effects (nausea, diarrhea, and vomiting) were most commonly reported in both groups with overall adverse events leading to early drug discontinuation in 11% of semaglutide patients and 9% of liraglutide patients. This study was funded in part by Novo Nordisk and did not include younger or older patients or patients with a high degree of diversity.

A 2017 RCT (N=388) assessed the efficacy of semaglutide monotherapy (0.5 mg or 1 mg weekly) versus placebo in patients with type-2 diabetes.[3] Patients were 54 years on average with a mean HbA1c of 8%, mean duration of DM of 4.2 years, 46% female, mean BMI of 33 kg/m^2, and were not on pharmacotherapy for DM 90 days before study entry. Primary outcomes were HgbA1C and weight reduction as well as adverse events reported (side effects and cardiovascular events). Mean body weight at week 30 significantly decreased with 0.5 and 1 mg doses of semaglutide compared with placebo (see **TABLE**). Nausea (20% and 24%) and vomiting (13% and 11%) were the most reported adverse events with semaglutide 0.5 mg and 1 mg. Some funding for this trial was received from Novo Nordisk. EBP

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Is venlafaxine an effective prophylactic medication for migraine headaches?

EVIDENCE-BASED ANSWER

Maybe. Venlafaxine seems to be an effective prophylactic medication for the reduction of migraine headache frequency (SOR: **B**, small clinical trials vs placebo or active agents). Venlafaxine is more effective than a combination of propranolol and nortriptyline (SOR: **C**, small randomized controlled trial [RCT]) and noninferior to amitriptyline (SOR: **C**, small RCT) for migraine frequency. However, venlafaxine may not be effective for reducing duration or severity of headaches (SOR: **C**, small RCT).

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A 2018 RCT (N=60) examined the effectiveness of venlafaxine for reduction of migraine frequency and severity compared with combination treatment of nortriptyline and propranolol.[1] Patients were nonpregnant adults without aura, experiencing at least three migraines per month and discontinued previous prophylactic medication two weeks before study admission. The intervention group (n=30) received venlafaxine 37.5 mg, once daily for 10 weeks, whereas the control group (n=30) received nortriptyline 25 mg once at night and propranolol 20 mg every 12 hours for 10 weeks. The primary outcomes measured were frequency and severity of headaches (0 to 10 scale, 10 worst pain), secondary outcomes were frequency of nausea, vomiting, and drowsiness episodes per month during the treatment period. Patients in the intervention group had a significant decrease in headache frequency (3.6 vs 4.0 per month, $P<.001$) and severity (6.2 vs 6.6,

$P<.001$). Patients in the intervention group also had fewer episodes of nausea (0.33 vs 0.43, $P<.001$) and vomiting (0.06 vs 0.13, $P<.001$) but more frequent episodes of drowsiness (0.57 vs 0.35, $P<.015$) per month. Limitations of this study include lack of demographical data, leading to questionable generalization of the results.

A 2005 RCT (N=60) evaluated the efficacy and safety of high-dose and low-dose venlafaxine compared with placebo for migraine prophylaxis in patients diagnosed with migraine without aura.[2] Patients were nonbreastfeeding adults experiencing 3 to 10 headache attacks per month for at least two years, had partial benefits from previous prophylactic medication, and had headaches severe enough to interfere with daily tasks and activities. Patients with major comorbidities and nonmigraine headache were excluded. Patients received extended release venlafaxine 150 mg (n=21), extended release venlafaxine 75 mg (n=20), or placebo (n=19) for 10 weeks. Outcomes measured included number of days with headache, severity of headaches using a 0 to 10 visual analogue scale (VAS) with higher scores indicating worsening severity, duration of headaches in hours, analgesic consumption, and adverse events recorded every two weeks. High-dose venlafaxine significantly reduced the mean number of days with headaches within 10 weeks compared with both the low-dose and the placebo group (mean difference [MD] –4 days vs –2 days vs –1 day, $P=.01$). No significant difference was observed between the three groups in headache severity (MD –4 vs –4 vs –1, $P=.07$) or in duration (MD –7 vs –7 vs –2 hours, $P=.48$). A significant decrease was noted in analgesic consumption in the low- and high-dose venlafaxine treatment groups compared with placebo (MD –5 and –4 vs 0, $P=.001$). No difference in side effects was observed between the groups at 10 weeks.

A 2004 randomized, crossover study (N=52) examined the prophylactic effect of amitriptyline compared with extended-release venlafaxine in patients with migraine with or without aura.[3] Patients were nonpregnant adults with median age of 32 years old, history of migraine for more than one year, and at minimum two attacks per month in the last three months. Patients with psychiatric disorders and major comorbidities were excluded from the study. In group 1 (n=26), patients received venlafaxine in the first treatment period (4–16 weeks) and amitriptyline in the second treatment period (20 to 32 weeks) for 36 weeks. In group 2 (n=26), patients received amitriptyline in the first treatment period and venlafaxine in second treatment period. During the first four weeks, patients received no prophylactic treatment and a four-week wash-out period was also noted between the two treatment periods. Venlafaxine was dosed as 37.5 mg/day for three days, 75 mg/day for 3 days, and 150 mg for 78 days. Amitriptyline was dosed as 10 mg/day for three days, 25 mg/day for three days, 50 mg/day for three days, and 75 mg/day for 75 days. Outcomes measured were number of migraine attacks, duration of attacks in hours, and severity of attacks graded on a 1 to 3 scale (1=able to work throughout the attack, 2=unable to work but not staying in bed, and 3= staying in bed) per month. Patients were followed up at four, 16, 20, 32, and 36 weeks. Both treatments improved symptoms significantly compared with baseline. However, patients in group one were similar to group two in headache frequency (3.6 vs 4.0, $P>.05$), severity (0.09 vs 0.01, $P>.05$), and all other major side effects per month. Patients in the amitriptyline groups experienced more side effects like hypersomnia (42 vs 6), difficulty concentrating (28 vs 3), and orthostatic hypotension (16 vs 1). EBP

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How safe are statins for treating children with familial hypercholesterolemia?

EVIDENCE-BASED ANSWER

Statins are quite safe. In children with confirmed familial hypercholesterolemia, there is no increased risk of serious adverse events with statin treatment compared with placebo (SOR: **A**, systematic review of randomized control trials [RTCs] and 2 prospective cohorts). Adverse effects were mild and do not result treatment discontinuation (SOR: **B**, 2 prospective cohorts).

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A 2017 systematic review of nine randomized controlled, double-blinded trials examined the effectiveness and safety of statin therapy in 1,155 children aged 4 to 18 years old with heterozygous familial hypercholesterolemia (FH).[1] Individuals included had elevated low-density lipoprotein-cholesterol (LDL-C), a Tanner stage of II or higher, a positive DNA diagnosis in a first-degree relative, and who personally had a positive DNA diagnosis. Those with diseases who could elevate lipids (eg, homozygous FH, diabetes mellitus, anorexia nervosa, kidney disorders, liver disorders, thyroid disorders, other dyslipidemias) or who were taking medications that could interact with statins (eg, immunosuppressants, cytochrome P-450 3A4–inducing drugs) were excluded. The treatment groups were treated with daily oral statins (lovastatin 40 mg, pravastatin 5–40 mg, simvastatin 20–40 mg, atorvastatin 10–20 mg, rosuvastatin 5–20 mg, or pitavastatin 1–4 mg), and the control groups were treated with placebo, other lipid-lowering therapy (eg, fibric acids or resins), or no intervention. The median intervention and follow-up time was 24 weeks. Compared with placebo or control groups, no significant increase was observed in the rate of adverse changes in growth and maturity (1 trial, n=211; risk ratio [RR], 0.95; 95%, CI 0.77–1.2), elevation of aspartate aminotransferase (7 trials, n=924; RR, 2.5; 95% CI, 0.29–20), or elevation of alanine aminotransferase (7 trials, n=924; RR, 2.0; 95% CI, 0.24–17) in children treated with statins. No reported cases of myopathy or rhabdomyolysis were observed, and the rates of other adverse events were not significant.

A 2015 prospective cohort study evaluated the safety of rosuvastatin therapy for two years in 198 children 6 to 17 years old with heterozygous FH.[2] Patients in the study had fasting LDL-C >190 mg/dL or a combination of LDL-C >158 mg/dL and another cardiovascular risk factor. Patients with a history of statin-induced myopathy were excluded. Participants were given initial daily 5-mg dosing, which was uptitrated with target LDL-C level of <110 mg/dL. Dosage increase was based on age group, with those 6 to 9 years (n=64) increased to 10 mg daily and those 10 to 17 years old (n=133) increased to 20 mg daily. Patients were followed for a treatment course of two years. Treatment-related adverse events and disturbances of normal growth and development were assessed. None of the participants deviated from normal curves of growth or sexual development. After two years, no severe adverse events were reported. Minor adverse events experienced were gastrointestinal upset (8%), myalgia (2%), elevated creatinine kinase (1%), and skin changes (1%).

A 2019 retrospective cohort study evaluated 131 children and adolescents 12 months to 14 years old with known or suspected FH to determine the safety and tolerance of intermediate-term statin therapy.[3] The median duration of treatment was four years. Patients were included if they had a family history of FH, failed to achieve a target goal despite at least six months of dieting and one of the following: possessed an LDL-C receptor, ApoB, a PCSK9 mutation, or an LDL-C level of greater than 190 mg/dL. Children homozygous for FH were excluded. Statin therapy was initiated when LDL-C remained greater than 160 mg/dL in the presence of another cardiovascular risk factor. Patients were monitored for self-reported side effects, including cramps, unexplained muscle pain, weakness, stiffness, asthenia, or abdominal pain. Minor side effects of asymptomatic creatinine kinase increases, myalgia, abdominal pain, dysuria, and diffuse pain were reported in 18% of patients. None of these events caused treatment discontinuation. Muscular side effects were observed in 12% of patients with 13% of those patients having an elevation in creatinine kinase. Elevations in alanine aminotransferase or aspartate aminotransferase greater than three times normal were not observed. No children had abnormalities of pubertal development during follow-up. EBP

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Is surgical versus conservative management more effective for displaced midshaft clavicle fractures?

EVIDENCE-BASED ANSWER

There is no difference in pain or function for displaced midshaft clavicle fractures treated operatively or nonoperatively (SOR: **A**; meta-analysis of randomized controlled trial [RCT]s). Surgery results in a lower risk of nonunion at 1 year, but there is no difference in rates of surgical revision between conservative management or surgical treatment (SOR: **A** meta-analysis of RCTs).

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In 2019, a meta-analysis evaluated 13 RCTs and one quasi-RCT comparing surgical versus conservative management of displaced or angulated midshaft fractures in adolescent or adult patients (N=1,469).[1] Patients included mostly men of 16–70 years old with mean ages in the studies between 27 and 39 years. Comparisons included plate or intramedullary fixation versus sling or figure-of-eight bandage. Time to surgical intervention ranged from 22 hours to 28 days. The primary outcomes were shoulder function or disability, pain as measured on a visual analog scale (0–100 mm, higher score indicating more pain, minimal clinically important difference 14 mm), and treatment failure (nonunion, malunion, or the need for a second procedure). Disability was measured using the arm, shoulder, and hand scale (DASH), scored from zero (no disability) to 100 (severe disability) with a minimal clinically important difference of 10 to 15. The Constant score (0–100) is a measure of pain and difficulty with activities of daily living (lower score indicates less pain and better function.). No difference was found between surgery and sling or figure eight bandage for upper arm function at one year or longer (10 studies, n=838; standard mean difference [SMD] 0.33, 95% CI, –0.02 to 0.67; evidence rated as low quality). No difference in pain was observed as measured by VAS at three months or at one year (3 studies, n=277; mean change, –0.08 mm; 95% CI, –3.6 to 3.5 and mean change, –0.6 mm; 95%, CI, –3.5 to 2.3; low-quality evidence). No difference was observed in disability on the DASH score at nine or more months (8 studies, n=896; mean difference [MD], –3.9 points; 95% CI, –7.8 to 0.01; I^2=90%). Function as measured by Constant score did show a small improvement favoring surgery, but this did not reach minimal clinically important difference at nine months or more (9 studies, n=867; MD, 3.8; 95% CI, 1.8–5.9). Surgery reduced the risk of treatment failure compared with sling or figure eight bandage (3.4% vs 12%; 12 studies, n=1,197; risk ratio [RR], 0.32; 95%, CI 0.2–0.5; low-quality evidence). Adverse events were higher in the surgical group compared with sling or figure eight bandage: infection or dehiscence (22/686 vs 0/641; RR, 5.6; 95% CI, 1.9–16), hardware irritation requiring removal (52/508 vs 1/483; RR, 9.8; 95% CI, 3.9–24), and skin or nerve problems (75/338 vs 17/310; RR, 4.9; 95% CI, 1.9–13).

A 2019 meta-analysis of 22 RCTs with 1,002 adults with minimum one-year follow-up compared operative plate fixation, intramedullary device, and nonoperative treatment for the treatment of midshaft clavicle fractures.[2] Of the 22 included trials, 10 overlapped with the previous meta-analysis. Mean age of patients was 37 years with 81% male, and the mean follow-up was 14 months. The primary was the chance of union at one year. Secondary outcomes included risk of revision surgery and functional outcome score. Operatively treated patients compared with nonoperatively treated showed greater rates of union (22 studies, n=1,965; 97 vs 89%; RR, 1.1; 95% CI, 1.1–1.2). In evaluating functional improvement, operative treatment did score higher on DASH and Constant scores at one-year, neither reached minimal clinical improvement difference (DASH number of studies and n not specified; MD, 3.8; 95% CI, 0.43–8.1; I^2=92% and Constant score 6 studies, n=not reported; MD, 4.5; 95% CI, 0.62–8.3; I^2=89%). Revision surgery was no different between

operative and nonoperative treatment (9 RCTs, n=not reported; odds ratio, 0.85; 95% CI, 0.31–2.5). EBP

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Is a figure of eight bandage better than a simple sling for midshaft clavicle fractures in adults?

EVIDENCE-BASED ANSWER

For midshaft clavicle fractures, there are no differences in pain level, shoulder function, rate of nonunion, or rate of clavicle shortening between arm sling and figure of eight bandage methods of treatment (SOR: **A**. meta-analysis of randomized controlled trials [RCTs] and cohort trial).

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A 2016 meta-analysis of four RCTs (N=416) evaluated conservative treatment of acute mid–third clavicle fractures[1]. Arm sling versus figure of eight bandage was compared in three trials with 296 patients. Most patients were male older than 14 years (median ages, 19, 25, and 32 years). All patients were randomized to shoulder immobilization in an arm sling or figure of eight bandage. The primary outcomes were shoulder function, pain, and treatment failure assessed using nonvalidated scoring scales. Functional outcomes were measured by the Constant score (0–100, with higher score indicating better outcome, minimally important clinical difference 10) and the American Shoulder and Elbow Surgeon Score (0–100 with higher score indicting better outcome, minimally important clinical difference was not provided). No difference was found in shoulder function at 6 to 12 months between a figure of eight bandage and an arm sling using either the Constant score, the American Shoulder and Elbow Surgeon Shoulder Score, and subjective "good function" (1 study, n=51; mean difference [MD], −0.75 points; 95% CI, –3.7 to 2.2, 1 study, n=51; MD, −1.7 points; 95% CI, –5.7 to 2.4, and 1 study, n=152; relative risk, 1.0; 95% CI, 0.96–1.04). Regarding pain, using a visual analogue scale where zero is no pain to 10 is the worst pain, there was no difference between a figure of eight bandage and an arm sling after the first week (2 studies, n=203; MD, 0.2; 95% CI, –0.32 to 0.73; I^2=0%) or the second week (MD, 0.43; 95% CI,–0.35 to 1.2; I^2=74%) of treatment. No difference was observed in rates of nonunion, shortening >15 mm, or pain at mean of 10 months (3 studies, n=264; risk ratio [RR], 9.5; 95% CI, 0.52–173, 1 study, n=51; RR, 1.01; 95% CI, 0.35–2.9, and 1 study, n=152; RR, 9.5; 95% CI, 0.52–173).

A 2020 retrospective cohort study examined length and functional outcomes and radiographic shortening in 60 adults with midclavicular fractures treated with figure of eight bandage or an arm sling for 4 to 6 weeks[2]. Patients were 67% male with a mean age of 39 years followed over a mean of 28 months. Evaluation was done via radiographs (used to determine clavicle shortening compared with noninjured clavicle), physical examination, and Constant Murley Shoulder Scores. The primary outcome was to amount shortening between the two groups, and the secondary outcome was shoulder function. After treatment, there was no difference in the mean percentage of clavicle shortening between an arm sling and a figure of eight bandage (12% vs 11%; *P*=.432). No difference was found in functional results between the groups (results and *P* value not provided). The relationship of shortening to function showed that in all patients, if shortening was less than 11% versus over 11%, the Constant Murley scores were statistically higher but did not reach the minimal clinical difference of 10 (83 vs 75; *P*=.001.) EBP

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In adults with type 2 diabetes mellitus, does a plant-based diet improve outcomes compared to usual diet?

EVIDENCE-BASED ANSWER

Probably. In patients with type 2 diabetes mellitus, plant-based diets reduce HgbA1c levels slightly more than omnivorous diets, but fasting blood glucose levels are not improved (SOR: **C**, disease-oriented evidence from a meta-analysis of randomized controlled trials [RCTs] and controlled trials). Plant-based diets lead to greater reductions in HbA1c, weight, total cholesterol, LDL, and urinary albumin compared with the American Diabetes Association (ADA) diet (SOR: **C**, disease-oriented evidence from single RCT).

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A 2014 meta-analysis of three RCTs, two controlled trials, and one randomized cluster trial (N=255) assessed the impact of a vegetarian diet on glycemic control in adults with type 2 diabetes mellitus.[1] Participants had an average HbA1c of 7.6%, a mean age of 53 years, and were 57% male. Participants had to be older than 19 years and on the diet for a minimum of four weeks. Studies were excluded if they used duplicate samples, multiple interventions, or included those with diabetes other than type 2. Intervention diets varied with four trials using a low-fat vegan diet, one trial using a regular vegan diet, and one trial implementing a lacto-ovo low-protein diet (vegetables, eggs, and dairy products). For the control diets, three trials used an omnivorous diet, one trial used a conventional diabetic diet, one used the 2003 ADA diet, and one used a regular low-fat diet. All six trials were pooled for analysis. Outcomes were assessed for a minimum of four weeks (mean, 24 weeks). Plant-based diets were associated with a small yet significant mean reduction in HbA1c (mean difference [MD], –0.39%; $P=.001$) compared with control diets. However, no significant reduction was observed in fasting blood glucose concentration between the plant-based diets and control diets (mean difference [MD], –0.36 mmol/L; $P=.30$). Limitations included small sample size, lack of randomization in some trials, and lack of consistency with control group diets.

A 2006 RCT (N=99) assessed the efficacy of a low-fat, vegan diet on glycemic control and cardiovascular risk factors for patients with type 2 diabetes mellitus.[2] Participants were predominantly Black, non-Hispanic (45%) or White, non-Hispanic (43%), female (55%), and were an average age of 57 years. BMI was over 30 kg/m^2 for 61% in the vegan group and 86% in the ADA group. Individuals with type 2 diabetes based on fasting plasma glucose greater than 6.9 mmol/L on two occasions or a prior diagnosis of type 2 diabetes with the use of hypoglycemic agents for at least the last six months before the study were included. Those with an HbA1c <6.5% or over 10.5%, those on insulin for>5 years, current substance abuse, pregnancy, or current use of a low-fat vegetarian diet were excluded. Each patient met with a registered dietician for one hour at the beginning of the study and attended one-hour weekly meetings with their assigned group for nutrition and cooking instruction. Patients in the intervention group were prescribed a vegan diet consisting of vegetables, fruits, grains, and legumes with a breakdown of 75% carbohydrates, 15% protein, and 10% fat. Patients in the control group were put on the 2003 ADA diet consisting of 60 to 70% carbohydrate and monounsaturated fats, 15 to 20% protein, less than 7% of saturated fat, and cholesterol intake under 200 mg/day. Outcomes

measured were HbA1c, plasma lipid level, urinary albumin, body weight, waist and hip circumference, and blood pressure at baseline and at 22 weeks. There was a significant reduction in the vegan group compared with the ADA diet group for HbA1c levels (–1.2% vs –0.4%; $P<.01$), overall body weight (–6.5 kg vs –3.1 kg; $P<.01$), total cholesterol (–0.87 vs –0.49 mmol/L; $P<.01$), and LDL levels (–0.58 vs –0.28 mmol/L; $P=.02$). The reduction in urinary albumin was also significantly greater in the vegan group (–16 vs –11 mg/24 hr; $P=.01$) compared with the ADA patients. Limitations identified in the study included reduced dietary adherence to the ADA diet compared with the vegan diet (44% vs 67%), as well as changes in medications during the study that may have confounded HbA1c interpretations. EBP

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In pregnant women with gestational diabetes mellitus, does insulin improve glycemic control versus the oral agents metformin and glyburide?

EVIDENCE-BASED ANSWER

Probably not. When comparing oral agents (metformin or glyburide) with insulin in gestational diabetes, no differences are seen in maternal fasting blood glucose or HbA1c levels (SOR: **C**, disease-oriented evidence from meta-analyses of RCTs and single randomized controlled trial [RCT]). No difference is seen in two-hour postprandial plasma glucose (2HPG) (SOR: **C**, disease-oriented evidence from one meta-analysis of RCTs and single RCT).

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A 2017 meta-analysis of 32 RCTs (n=4,723) measured 2HPG, fasting blood glucose, and HbA1c in gestational diabetics treated with metformin and glyburide versus insulin.[1] Patients with singleton pregnancies, ranging from 18 to 45 years, and who failed diet and exercise were included in the studies. Patients were excluded for preexisting conditions, including diabetes, renal, cardiac, or hepatic disease. Other exclusion criteria included high-risk obstetrics classification, intolerance to diabetic medications, and treatment with oral steroids. Participants were diagnosed with gestational diabetes between 11- and 36-week gestation. Diagnosis was confirmed with 50 to 100 g oral glucose tolerance tests or by a home capillary glucose monitoring device. Treatment groups included metformin 500 to 7,500 mg per day, starting insulin dose ranging from 0.2 to 1 units per kilogram per day and glyburide 0.625 to 20 mg per day. Glycemic control targets included fasting blood glucose of 90 mg/dL or less, two-hour postprandial glucose of 120 mg/dL or less, and HbA1c levels of 6% or lower. Oral agent treatment groups either added or switched to insulin if glycemic control was not obtained. Results were pooled and converted into standardized mean differences (SMD) in a network meta-analysis. A network meta-analysis examines more than two groups of treatment for an outcome. When comparing all three treatments, no significant difference was observed in 2HPG (6 trials, n=1,345; SMD, –0.99; 95% CI, –2.0 to 0.001), fasting blood glucose levels (17 trials, n=2,769; SMD, –0.03; 95% CI, –0.41 to 0.32), or HbA1c levels (17 trials, n=2,887; SMD, 0.17; 95% CI, –0.22 to 0.56).

A 2019 RCT (n=286) evaluated fasting blood glucose, 2HPG and HbA1c in groups of patients with gestational diabetes treated with insulin versus metformin.[2] Participants

were women with singleton pregnancies, ranging in age from 18 to 40 years, diagnosed with gestational diabetes mellitus at 24 to 28 weeks. Women were included if they failed diet and exercise and excluded if they had preexisting diabetes, renal or hepatic disease, increased risk for lactic acidosis, known fetal anomalies, unresponsiveness to metformin or refusal to attend appointments. Women were randomized to receive either insulin (n=143) or metformin (n=143). Patients were diagnosed with the 75-g oral glucose tolerance test. Treatment included metformin 500 to 1,500 mg per day or insulin 0.1 units per kilogram per day. Glycemic control targets aimed to reduce fasting blood glucose to 95 mg/dL or lower and an 2HPG of less than 120 mg/dL. HgA1c did not have a target goal but was checked monthly starting at an average of 24 weeks and ending eight weeks after delivery. No significant difference was observed in reductions in fasting blood glucose (91 vs 92 mg/dL; *P*=.57), 2HPG levels (152 vs 153; *P*=.69), and HbA1c levels (5.4% vs 5.6%; *P*=.79) for patients treated with metformin compared with those in the insulin group. EBP

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Are oral steroids effective in the management of chronic rhinosinusitis in adults?

EVIDENCED-BASED ANSWER

Yes, oral steroids alone or in combination with other steroid treatment modalities (intranasal, nebulized) improve patient symptoms and reduce polyp size with a short course of therapy (≥21 days) (SOR: **A**, based on consistent data from a systematic review of small randomized controlled trials [RCTs] and two additional small RCTs).

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A 2016 systemic review (8 RCTs; N=474) compared short course oral corticosteroids with placebo or no intervention in adult patients with chronic rhinosinusitis with nasal polyps.[1] Participants had a mean age of 46 years (67% male) and chronic rhinosinusitis with nasal polyps and symptoms for at least 12 weeks. The trials used oral prednisolone equivalence of 25 to 60 mg per day. Disease-specific health-related quality of life (rhinosinusitis outcome measure that measures six nasal symptoms [congestion, rhinorrhea, sneezing, hyposmia, postnasal discharge, and thick nasal debris]) scores improved with oral corticosteroids (RCT=1, n=40; standardized mean difference [SMD], –1.24; 95% CI, –1.92 to –0.56) compared with placebo after 2 to 3 weeks of treatment. Disease severity (patient reported score from blocked nose, rhinorrhea, hyposmia, and sinonasal pain assessed on a 7-point Likert scale) improved from baseline (RCT=1, n=67; SMD, –2.28 95% CI, –2.76 to –1.80) compared with placebo after 14 days. Disease severity improvement was improved after a two-week course of oral steroids and nasal steroids compared with intranasal steroids alone (RCT=1; n=114; SMD, –2.28; 95% CI, –2.75 to –1.8); however, it was not maintained at the three-month follow-up (RCT=1; n=114; SMD, –0.22; 95% CI, –0.59 to 0.15). A meta-analysis was not performed because of significant heterogeneity among studies. This review was limited by poorly defined diagnostic criteria of rhinosinusitis and nasal polyps.

A 2019 randomized control trial (N=84) compared the efficacy and safety of steroids administered through different routes in patients with chronic rhinosinusitis with nasal polyps.[2] Patients were adults between 23 to 64 years (mean age, 43) and were predominately male (55%) from a single outpatient clinic. All patients had symptoms (nasal blockage/

discharge, loss of smell, headache/facial pain) for at least 12 weeks and sinusitis confirmed by computed tomography. Polyps were confirmed by nasal endoscopy with greater than 54% eosinophils in polyp tissue biopsy. Patients received a two-week course of oral prednisolone (0.5 mg/kg per day), nebulized budesonide (1 mg twice daily), or intranasal budesonide (256 μg twice daily). The primary outcome was the total nasal symptom score (TNSS), calculated as the sum of four patient-reported nasal symptoms (olfactory, rhinorrhea, facial pain/headache) using a scale of 0 to 10 (increasing with severity). Posttreatment TNSS scores improved for both oral (4.9 vs 2.9; $P<.001$) and nebulized (4.7 vs 3.3; $P<.001$) groups but not for the intranasal group (data not provided). This study reported limited statistical analysis.

A 2013 randomized control trial (N=45) compared the use of a short course of oral corticosteroids in addition to intranasal corticosteroids against nasal steroid use alone in adults with chronic rhinosinusitis and nasal polyps.[3] Participants had a mean age of 34 years and 56% male from a single hospital in Turkey. Polyp size was measured by endoscopic appearance using the Rasp criteria (graded from 1 to 4, least severe to most severe). Polyp size decreased more in patients taking a combination of oral steroids (1 mg/kg oral methylprednisolone titrated over 21 days) and nasal steroid (400 μg/day of budesonide over 21 days) compared with nasal steroids alone (mean difference, –0.46; 95% CI, –0.87 to –0.05). The study was limited by the short-term nature of the assessed outcomes. EBP

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Are SSRIs an effective pharmaceutical treatment for depression in adolescents?

EVIDENCE BASED-ANSWER

SSRIs are an effective pharmaceutical treatment for major depression in adolescents. (SOR: **A**, 3 high-quality randomized controlled trials [RCTs]). SSRIs may have greater efficacy than tricyclic antidepressants in the treatment of depression in adolescents (SOR: **B**, single RCT).

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A 2009 multicenter, randomized, double-blind, placebo-controlled trial (N=316) compared the safety and efficacy of escitalopram with placebo in adolescents with major depression.[1] Participants included were between 12 and 17 years old and met the Diagnostic and Statistical Manual of Mental Disorders-4 (DSM-IV) criteria for major depression within the past 12 weeks. Adolescents were excluded if they possessed other mental disorders, such as bipolar disorder, psychosis, and the like. Patients were randomized to receive either 10 to 20 mg per day of escitalopram (n=155) or placebo (n=157) for a total of eight weeks. Efficacy was measured as a change from baseline at week eight in the Children's Depression Rating Scale-Revised (CDRS-R; scored 17–113 using the last observation carried forward approach). Significant improvement was seen in the escitalopram group versus the placebo group at end point in CDRS-R score (least squared mean difference [LSMD], –3.4; P=.02) (The LSMD is generally close to the arithmetic mean, but it is used when there are missing data or risk adjustments). Rates of discontinuation as a result of adverse events did not differ between the two groups. Possible biases include sponsorship for the study by Forest Laboratories, manufacturer of escitalopram, who also collected and analyzed the statistical data.

A 2002 multicenter, randomized, controlled trial (N=219) evaluated the efficacy of a fixed dose of 20 mg of fluoxetine in children and adolescents with major depressive disorder.[2] Patients had a mean age of 13 years, a minimum score of four on the Clinician's Global Impression (Severity) scale, and a CDRS-R score above 40. After a one-week lead in, patients were randomized to receive either 10 mg per day fluoxetine or placebo, starting with fluoxetine 10 mg/d for one week, and then fluoxetine 20 mg/d for eight weeks or placebo. After nine weeks, there was a significantly greater improvement in mean change of CDRS-R scores for the intervention group compared with the control group (35 vs 40 points; P<.05). The prospectively defined criteria for remission was met more often in the fluoxetine-treated group (41% vs 20%; P<.01). There was no significant difference between treatment groups for discontinuation because of adverse events.

A 2001 multicentered, double-blinded, randomized, parallel-design trial (N=275) compared paroxetine with placebo versus imipramine with placebo for the treatment of adolescent depression.[3] Participants were 12 to 18 years old, and all had met criteria for major depression for at least the last eight weeks via the Diagnostic and Statistical Manual of Mental Disorders-4 (DSM-IV). Those with other significant mental disorders were excluded. Adolescents were randomized to twice daily paroxetine 20-40 mg (n=93), twice daily imipramine with a gradual titration to 200 to 300 mg (n=95), or placebo (n=87). Efficacy was measured by a score of eight or less or a 50% reduction in baseline on the Hamilton Rating Scale for Depression (HAM-D) and overall scores on the HAM-D. Patients treated with paroxetine achieved a HAM-D score of eight or less at a significantly higher rate compared with placebo (63% vs 46%; P=.02). However, the imipramine group did not have a significant difference in achievement rate compared with placebo (50% vs 46%; P=.57). The dropout rate of patients treated paroxetine was similar to the placebo rate (9.7% vs 6.9%; P=.5) but was significantly higher in the imipramine group (32% vs 6.9%; P<.01). Of note, adolescents withdrawing from imipramine therapy because of complications, nearly one third did so because of adverse cardiovascular effects. EBP

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