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EVIDENCE-BASED PRACTICE

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FPIN
Family Physicians Inquiries Network

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SPOTLIGHT ON PHARMACY

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

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STATEMENT OF PURPOSE

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

DISCLOSURE
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Do lesbian, gay, bisexual, transgender, and questioning individuals have a higher prevalence of tobacco use than their cisgender or heterosexual counterparts?

EVIDENCE-BASED ANSWER

Lesbian, gay, bisexual, transgender, and questioning (LGBTQ) individuals are up to twice as likely to use tobacco products compared with heterosexual and cisgender individuals. Transgender individuals may be more likely to use tobacco compared with cisgender individuals, although this effect may diminish with adjustment for other sociologic variables. Bisexual women are more likely to use tobacco, even compared with other LGBTQ individuals (SOR: **B**, cross-sectional studies).

DOI 10.1097/EBP.0000000000001363

A 2018 cross-sectional cohort study (N=198,057) evaluated the relationship between sexual and gender identity and tobacco use using data collected through the Behavioral Risk Factor Surveillance System.[1] The study included adults 18 years old and older who were asked through a random digit dial phone survey whether they had "ever smoked" (defined as more than 100 cigarettes in a lifetime) or "currently smoked." Of the participants, 708 (0.36%) identified as transgender and were further asked to identify as male-to-female, female-to-male, or gender nonconforming. Sexual minorities were determined by asking participants if they identified as straight, lesbian or gay, or bisexual; 6,450 participants (3.3%) identified as a sexual minority. Answers of "other," "don't know," or "refuse" were excluded. Lesbian and gay adults were more likely than straight adults to ever smoke cigarettes (unadjusted odds ratio [OR] 1.2; 95% CI, 1.1–1.4) and currently smoke (unadjusted OR 1.5; 95% CI, 1.3–1.7). Transgender adults were significantly more likely to currently smoke (unadjusted OR 1.5; 95% CI, 1.1–2.1), but after adjustment for demographics, socioeconomic status, and other unhealthy behaviors, the difference between transgender and cisgender individuals was no longer statistically significant. This study was limited by small sample size of both gender and sexual minorities, as well as lack of national representation (only 26 states were surveyed).

A 2016 cross-sectional cohort study (N=57,994), using data from the 2012 to 2013 National Adult Tobacco Survey, compared smoking rates of lesbian, gay and bisexual with heterosexual individuals.[2] Participants were over 18 years old with interviews completed via a random digit dial phone survey of landlines and cell phones; 2,026 respondents identified as lesbian/gay, bisexual, or "something else." Respondents were asked "Have you smoked at least 100 cigarettes in your entire life?" and "Do you now smoke cigarettes every day, some days, or not at all?". Respondents who currently smoked every day or some days and reported smoking 100 cigarettes or more in their lifetime were recorded as current smokers. Prevalence estimates were calculated for frequency of cigarette use and quit attempt in the past 12 months. Overall, current cigarette smoking was higher in sexual minority groups compared with straight individuals (27% vs 17%; $P<.001$). Smoking prevalence varied significantly among subgroups. Among women, prevalence of current cigarette smoking was 14% for women who identified as straight, 22% for those who identified as lesbian/gay ($P<.05$ compared with straight women), and 36% for those who identified as bisexual ($P<.05$ compared with straight women). Among men, the prevalence of cigarette smoking was 26% for those who identified as gay and 21% for those who identified as straight ($P<.05$). The prevalence of sexual minorities in this sample size was lower compared with more comprehensive demographic surveys. Small sample sizes limited the ability to examine patterns of tobacco use based on certain demographic characteristics.

A 2017 cross-sectional cohort online survey study (N=17,372) examined past 30-day use of cigarettes, cigars, and e-cigarettes in transgender individuals independent of sexual orientation.[3] The study included

17,164 cisgender and 168 transgender individuals, 18 years old and older who were recruited via random digit dialing supplemented by address-based sampling. Tobacco users were oversampled to provide adequate sample size for the group. Participants were excluded if they failed to report their gender identity. Transgender adults had a higher past 30-day use of any tobacco product (40% vs 25%, $P \leq .003$) and current use of cigarettes (36% vs 21%, $P \leq .003$) compared with cisgender adults. Transgender individuals had significantly higher odds of past 30-day tobacco use for any product (OR 2.0; 95% CI, 1.3–3.1) compared with cisgender individuals. Limitations included a small sample size that precluded subgroup analysis beyond gender. Because the study included only a single question identifying gender and did not specify between sex assigned at birth and current gender, the analysis based on male/female categorization likely has crossover between gender groups and excluded nonbinary individuals. EBP

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The authors declare no conflicts of interest.

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Extended direct oral anticoagulation prophylaxis after hospital discharge is superior to placebo in preventing thromboembolism

Bhalla V, Lamping OF, Abdel-Latif A, Bhalla M, Ziada K, Smyth SS. Contemporary meta-analysis of extended direct-acting oral anticoagulant thromboprophylaxis to prevent venous thromboembolism. *Am J Med.* 2020; 133(9):1074–1081.e8.

DOI 10.1097/EBP.0000000000001259

This meta-analysis and systematic review of four phase III randomized controlled trials (N=26,408) examined the efficacy and safety of six weeks of a direct oral anticoagulant (DOAC) for postdischarge thromboprophylaxis compared with placebo in nonsurgical hospitalized patients with risk factors for thrombosis. Patients had a discharge diagnosis of congestive heart failure New York Heart Association class III or IV, active cancer, acute ischemic stroke, acute respiratory failure, or infectious or inflammatory disease. After 6 to 10 days of enoxaparin prophylaxis in-hospital, patients were assigned to placebo or a reduced intensity regimen of rivaroxaban 10 mg daily, apixaban 2.5 mg twice daily, or betrixaban 80 mg daily for 30 to 45 days. The primary outcome was the composite of total venous thromboembolism (VTE) and VTE-related death. The secondary outcome was the incidence of nonfatal symptomatic VTE. The primary safety outcome was the incidence of major bleeding. The primary outcome occurred in 2.9% of patients in the DOAC group compared with 3.6% of patients in the placebo group (odds ratio [OR] 0.79; 95% CI, 0.69–0.91; $P<.01$). The secondary outcome occurred in 0.48% of patients in the DOAC group compared with 0.77% of patients in the placebo group (OR 0.62; 95% CI, 0.47–0.83; $P<.01$). Major bleeding occurred in 0.58% of patients in the DOAC group compared with 0.30% of patients in the placebo group (OR 1.9; 95% CI, 1.4–2.7; $P<.01$). Nonmajor bleeding was similar (2.2% vs 1.2%; OR 1.8; 95% CI, 1.5–2.1; $P<.01$). The number needed to treat (NNT) with a DOAC for 30 to 45 days after discharge to prevent a nonfatal symptomatic VTE is 345, and NNT to prevent a fatal VTE is 899 patients. For major bleeding, the number needed to harm (NNH) with DOAC use is 3089, whereas the NNH for clinically relevant nonmajor bleeding was 110 patients. Cost-benefit analysis also favored extended DOAC use.

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

Bottom Line: Extended thromboprophylaxis with a DOAC after nonsurgical hospital discharge efficiently reduces VTE events, improves mortality, and lowers costs. Patients in this study had serious medical illness and risk factors for thrombosis, and results may not be generalizable to hospitalized patients at lower risk.

Methods

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

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The author declares no conflicts of interest.

Repeating bone mineral density screening after 3 years does not improve fracture risk prediction

Crandall CJ, Larson J, Wright NC, et al. Serial bone density measurement and incident fracture risk discrimination in postmenopausal women [published online ahead of print, 2020 Jul 27]. JAMA Intern Med. 2020; 180(9):1232–1240.

DOI 10.1097/EBP.0000000000001257

A multicenter prospective cohort study compared repeat bone mineral density (BMD) testing 3 years after baseline screening to no additional testing for predicting future risk of hip or major osteoporotic fracture (MOF) in postmenopausal women (N=7419 women, from a Women's Health Initiative sub-study on bone density). At the time of repeat BMD testing, patients had a mean

age of 66.1 years (range, 50–79 years at enrollment; 44% younger than 65 years), mean BMI of 28.7 kg/m^2, and were 23% non-white. Women were excluded from the study if they were treated with medications other than vitamin D and calcium, missed follow-up after 3-year BMD, reported a history of MOF at baseline or between BMD testing, or if covariate data were missing. Approximately 3% of patients had osteopenia (T score≤2.5). Fractures were self-reported on annual questionnaires and hip fractures confirmed using medical records. During the study follow-up (mean, 9 years after second BMD measurement), 139 women (1.9%) experienced one or more hip fractures and 732 women (9.9%) experienced one or more major osteoporotic fractures.

Area-under-the-receiver-operating-characteristic (AU-ROC) curve values for baseline BMD screening and baseline plus 3-year BMD were similar in their ability to discriminate women who would experience hip fracture or MOF from women who would not. The AU-ROC to predict future hip fracture was 0.71 (95% CI, 0.67–0.75) for baseline total hip BMD, 0.61 (95% CI, 0.56-0.65) for change in total hip BMD between baseline and 3-year BMD, and 0.73 (95% CI, 0.69-0.77) for the combination of baseline total hip BMD and change in total hip BMD. AU-ROC values for femoral neck BMD and lumbar spine BMD for the discrimination of hip fracture and of MOF were very similar to those for total hip BMD. The AU-ROC values were similar among age subgroups (<65 years, 65–74 years, ≥75 years). Associations between change in bone density and fracture risk did not change when adjusted for factors, including diabetes, race/ethnicity, body mass index, or baseline BMD.

Methods

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

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

Bottom Line: Repeat BMD testing at three years does not improve hip or MOF risk prediction in postmenopausal women beyond that of the initial screening. Associations between bone density and future fracture risk were the same when adjusted for risk factors, including diabetes, age, race and ethnicity, baseline BMD, and BMI. BMD testing should not be repeated at three years in women who do not initially require treatment of low bone density.

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The authors declare no conflicts of interest.

Potential association between initiation of pulmonary rehabilitation within 90 days after hospitalization for COPD and improved 1-year all-cause mortality

Lindenauer PK, Stefan MS, Pekow PS, et al. Association between initiation of pulmonary rehabilitation after hospitalization for COPD and 1-year survival among medicare beneficiaries. *JAMA*. 2020; 323(18):1813-1823.

DOI 10.1097/EBP.0000000000001320

Investigators performed a retrospective cohort study on claims data for fee-for-service Medicare beneficiaries hospitalized with COPD. They examined the relationship between initiation of pulmonary rehabilitation within 90 days of discharge and 1-year all-cause mortality. A total of 197,376 patients (mean age 76.9 years old, and 58.6% female) were enrolled, with 2,721 (1.5%) of those patients initiating pulmonary rehabilitation within 90 days of hospital discharge. The study excluded patients who underwent pulmonary rehabilitation within the year prior, hospitalizations over 31 days, discharge to long-term care facilities, deaths within 30 days of discharge, and medical conditions that limit utilization of rehabilitation. Total deaths in the cohort in one year was 38,302 (19.4%), with mortality in 198 (7.3%) of those who initiated pulmonary rehabilitation within 90 days of discharge. One-year survival was associated with initiation of pulmonary rehabilitation within 90 days with an absolute risk difference –6.7% (95% CI, –7.9% to –5.6%);

hazard ratio 0.63 (95% CI, 0.57 to 0.69). The population of patients who enrolled in pulmonary rehabilitation within 90 days was younger (mean 74.5 vs 77 years), more often men (47.6% vs 41.3%), more often non-Hispanic white (92.6% vs 85.1%), lived closer to rehabilitation facility (mean 5.8 vs 9.8 miles), were more likely to have no previous admissions (61.9% vs 52.4%), but were more likely to receive home oxygen therapy before hospitalization (39.4% vs 31.7%).

Methods

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

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

Bottom line: This study demonstrates a possible association between initiation of pulmonary rehabilitation within 90 days of hospital discharge after admission for COPD and improved 1-year all-cause mortality. Similar to previous small meta-analyses, this study's conclusions are influenced by multiple variables. A large, prospective, randomized controlled trial is needed to support the benefit of early pulmonary rehabilitation after COPD exacerbation.

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Anticoagulation and antiplatelet therapy for stable CAD? As good as it sounds?

Bhatt DL, Eikelboom JW, Connolly SJ, et al. Role of Combination Antiplatelet and Anticoagulation Therapy in Diabetes Mellitus and Cardiovascular Disease: Insights From the COMPASS Trial. *Circulation*. 2020;141(23): 1841-1854.

DOI 10.1097/EBP.0000000000001329

This post-hoc analysis of the COMPASS trial (a double-blind randomized controlled trial [RCT]) compared cardiovascular outcomes in diabetic patients on low-dose rivaroxaban with aspirin versus placebo with aspirin.

The COMPASS trial was a multicenter, multi-country RCT of 27,395 patients with stable coronary artery disease (CAD) or peripheral artery disease (PAD) comparing 5 mg rivaroxaban twice daily (BID) versus acetylsalicylic acid (ASA) plus 2.5 mg rivaroxaban BID versus ASA plus placebo. Patients deemed to have higher risks of bleeding, such as recent intracerebral hemorrhage, or who met criteria for full anticoagulation were excluded. This subgroup analysis identified 6,922 patients from the COMPASS trial with diabetes and 11,356 patients without diabetes from the intervention (rivaroxaban plus ASA, n=9,152) and control (placebo plus ASA, n=9,126) arms. The primary efficacy endpoints were cardiovascular death, myocardial infarction, stroke, and a composite of these over the 36-month trial period. Secondary outcomes included all-cause mortality and all major vascular events. The primary safety endpoint was major bleeding events. In both groups, a similar composite relative risk reduction was noted for patients on rivaroxaban plus aspirin in both the diabetic and the nondiabetic groups (diabetes hazard ration [HR] 0.74; 95% CI, 0.61–0.90, number needed to treat [NNT]=44; and nondiabetes HR 0.77; 95% CI, 0.64–0.93, NNT=73). However, despite the apparent absolute risk reduction in all-cause mortality for diabetic patients compared with nondiabetic patients (absolute risk reduction 1.9 vs 0.6, $P_{\text{interaction}}=.02$), because of the higher baseline risk for those with diabetes,

the authors stated both groups ultimately derived similar benefits in NNT. Furthermore, a statistically significant increased risk of bleeding was noted in both groups (diabetes HR 1.7; 95% CI, 1.3–2.3; number needed to harm [NNH]=76; and non-diabetes HR 1.7; 95% CI, 1.3–2.2; NNH=80).

Methods

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

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

Bottom line: Although a reduction in the absolute risk of adverse cardiovascular outcomes was noted for diabetic patients with stable CAD or PAD on low-dose rivaroxaban with aspirin, this benefit was offset by the increased risk of significant bleeding events. The study demographics may not adequately represent the diversity of patients seen in primary care in the United States (only 1% of patients were identified as Black), and there may still be cost concerns for patients starting long-term direct oral anticoagulants. For patients with stable CAD or PAD, the COMPASS trial overall suggested benefit with low-dose rivaroxaban and aspirin therapy; however, whether the diabetic subgroup's benefits outweighs treatment risk will require further investigation.

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The authors declare no conflicts of interest.

Robotic versus laparoscopic, for patient or for practice?

Robotic inguinal versus transabdominal laparoscopic inguinal hernia repair: the RIVAL randomized clinical trial

Prabhu AS, Carbonell A, Hope W, et al. Robotic Inguinal versus Transabdominal Laparoscopic Inguinal Hernia Repair: The RIVAL Randomized Clinical Trial. *JAMA Surg.* 2020. doi: 10.1001/jamasurg.2020.0034.
DOI 10.1097/EBP.0000000000001180

KEY TAKEAWAY: Robotic inguinal repairs, compared with laparoscopic repairs, have similar patient postoperative pain, quality of life, mobility, scarring, and wound healing, despite higher cost, surgeon frustration, surgeon work, and longer operating times.
STUDY DESIGN: Prospective, single-blinded randomized clinical trial.
LEVEL OF EVIDENCE: STEP 3.

BRIEF BACKGROUND INFORMATION: Popularity of robotic over laparoscopic surgeries is rising because of claims of decreased postoperative pain and improved surgeon ergonomics, without direct trials between the techniques.

PATIENTS: Patients 21 years old and older undergoing unilateral inguinal hernia repair without history of open abdominal surgery nor preperitoneal mesh, and BMI $\leq$40 kg/m^2.
INTERVENTION: Robotic transabdominal preperitoneal inguinal hernia repair.
CONTROL: Laparoscopic transabdominal preperitoneal inguinal hernia repair.
OUTCOME: Patient outcomes: postoperative pain, health-related quality of life, mobility, wound healing, and scarring.

SYSTEM OUTCOMES: Surgeon ergonomics, and surgeon workload.

METHODS BRIEF DESCRIPTION:
- This patient blinded prospective randomized clinical study was conducted from April 2016 to 2019 in 6 U.S. hospitals. Transabdominal preperitoneal hernia repairs performed by attending surgeons on patients 21 years old and older with body mass index $\leq$40 kg/m^2, for first or recurrent unilateral inguinal hernias, without history of open abdominal surgery or mesh in preperitoneum. Exclusion criteria were open, strangulated, or bilateral repairs, patients with advanced liver or renal disease, or those unable to give consent. Patients were randomly assigned to robotic or laparoscopic surgery and were asked on follow-up to rank pain using visual analogue scale (VAS 0–100, 0=no pain and 100=worst pain), mobility using Physical Activity Assessment Tool, scarring using Stony Brook Scar Evaluation Form, and quality of life using 36-Item Short Form Health Survey (SF-36). After each case, surgeons reported perceived mental workload using NASA Task Load Index Scale (NASA-TLX; 1–100, lower=lower workload) and ergonomics using Rapid Upper Limb Assessment (RULA; 5–6=increased risk of musculoskeletal injury, $\geq$7=imminent risk of injury). Costs included total, operating room, and materials.

INTERVENTION (# IN THE GROUP): 48.
COMPARISON (# IN THE GROUP): 54.

FOLLOW UP PERIOD: Preoperative, 1 week, and 1 month postoperative.

RESULTS: Patient-reported outcomes at preoperative (pain VAS 18.8 laparoscopic vs 15.2 robotic; P=.42), 1 week postoperative (VAS 4.60 vs 5.53; P=.86), and 1 month postoperative visits (VAS –7.92 vs –7.00 [from baseline]; P=.85) were all similar.
- Increased frustration (NASA-TLX 32.7 robotic vs 20.1 laparoscopic, P=.004), effort (NASA-TLX 36.7 vs 27.4, P=.05), and mental workload (NASA-TLX 27.5 vs 21.9, P=.10) reported by surgeons for robotic repairs, with worse upper limb ergonomics (RULA left: 10.3 vs 9.8, P=.31, right: 10.2 vs 10.1, P=.94).
- Similar 30-day wound morbidity and overall adverse events (including superficial site infections, purulent drainage, urinary retention), and unanticipated hospital admissions, despite higher cost and longer operating time (including dissection of hernia, mesh fixation, and peritoneal closure).

LIMITATIONS:
- Pilot study, required only 25 cases minimum to be proficient.

- Only studied preoperative, 1 week postoperative, and 1 month postoperative.
- Journal results for pain is different from those in supplemental (eTable4). EBP

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The author declares no conflicts of interest.

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Is routine CSF testing of infants with a positive UA necessary?

Testing for meningitis in febrile well-appearing young infants with a positive urinalysis

Wang ME, Biondi EA, McCulloh RJ, et al. Testing for meningitis in febrile well-appearing young infants with a positive urinalysis. *Pediatrics*. 2019; 144(3): e2083979 DOI 10.1097/EBP.0000000000001199

KEY TAKEAWAY: In infants seven to 60 days old with a positive urinalysis and treated for UTI without cerebrospinal fluid (CSF) testing, no cases of delayed meningitis were diagnosed within seven days of discharge. Routine CSF testing in these infants may not be necessary.
STUDY DESIGN: Retrospective cohort study (N=20,570).
LEVEL OF EVIDENCE: STEP 3.

BRIEF BACKGROUND INFORMATION: Infants with a positive urinalysis are typically considered "high risk" and CSF evaluation is recommended. Risk factors associated with CSF testing in infants with positive urinalysis and risk of delayed diagnosis of bacterial meningitis in patients without CSF testing is unknown.

PATIENTS: Well-appearing febrile (≥38°C) infants seven to 60 days old with a positive urinalysis who received treatment for UTI after presenting to the emergency or inpatient setting with no comorbidities or diagnosis of bronchiolitis and not transferred to/from another facility.
INTERVENTION: CSF testing.
CONTROL: No CSF testing.
OUTCOME: Primary: Diagnosis of delayed meningitis.
SECONDARY: Risk factors associated with CSF testing.

METHODS BRIEF DESCRIPTION: Data obtained from 124 hospitals participating in the American Academy of Pediatrics quality improvement project, Reducing Excessive Variability in Infant Sepsis Evaluation. Age was divided into seven to 30 and 31 to 60 days of age. These groups were examined for factors associated with CSF testing and evaluated for delayed meningitis via chart review from September 2015 to November 2017.

INTERVENTION (# IN THE GROUP): 2,511.
COMPARISON (# IN THE GROUP): 1,061.

FOLLOW UP PERIOD: Delayed meningitis: diagnosis within seven days of the date of treatment or hospital discharge.

RESULTS:
PRIMARY OUTCOME:
- 3,572 infants had a positive urinalysis, 2,511 (70.3%) underwent CSF testing ranging from 64% to 100% for infants seven to 30 days old and 10% to 100% for infants 31 to 60 days old.
- In infants with a positive urinalysis, without CSF testing, who were treated for urinary tract infection, no cases of delayed meningitis (0%; 95% CI, 0%–0.6%) were noted; however, these infants were predominantly aged 31 to 60 days.

SECONDARY OUTCOME:
- Infants with positive UA received CSF testing more frequently than infants with negative UA (70.0% vs 58.1%, $P<.001$); however, no significant difference was noted in the percentage treated for bacterial meningitis (0.7% vs 0.9%, $P=.37$).
- Factors that increased likelihood of CSF testing included being seven to 30 days of age (adjusted odds ratio [aOR] 4.6; 95% CI, 3.8–5.5), abnormal inflammatory markers (aOR 2.2; 95% CI, 1.8–2.5), and setting of

hospitals with >300 febrile infants per year (aOR 1.8; 95% CI, 1.2–2.6).

LIMITATIONS:

- Risk of discrepancy in interrater reliability for outcome assessment.
- Detailed data on patients not collected potentially impacting regression analysis.
- Inflammatory marker testing inconsistent across sites.
- Delayed meningitis may have presented after the seven-day follow-up.

EBP

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The author declares no conflicts of interest.

What are the common side effects of glucagon-like peptide 1 agonists in older adults with diabetes?

CASE PRESENTATION

You are seeing a 71-year-old woman with type 2 diabetes mellitus and obesity currently on metformin monotherapy. She feels she has maximized therapeutic lifestyle changes and her HbA1c is persistently 8.5% to 8.7%, with a goal of less than 8.0%. She is otherwise healthy. She has read about glucagon-like peptide 1 (GLP-1) agonists that could reduce her weight but is concerned about possible side effects. She asks which side effects are most common with these medications.

DOI 10.1097/EBP.0000000000001393

Bottom Line

When treating type 2 diabetes in older adults, common side effects of GLP-1 agonists include weight loss, nausea, vomiting, diarrhea, and hypoglycemia. The frequency of most side effects is similar in patients >65 years old when compared with younger patients, but hypoglycemia seems more common in older patients when a GLP-1 agonist is added to insulin or a sulfonylurea.

Evidence Summary

An industry-funded retrospective pooled analysis of five randomized controlled trials (RCTs; N=5,171) examined the efficacy and safety of once-weekly dulaglutide in patients with type 2 diabetes, comparing those 65 years old and older (n=958, 19%) with those <65 years old.[1] The included RCTs evaluated the efficacy and safety of dulaglutide as monotherapy and in combination with other antihyperglycemics compared head-to-head against other antihyperglycemics over 26 weeks (258 patients ≥65 years old received dulaglutide 0.75 mg weekly and 318 patients ≥65 years old received dulaglutide 1.5 mg weekly). The reported outcomes included change in HbA1c, change in weight, rates of hypoglycemia, and rates of gastrointestinal adverse effects. Weight loss data were reported graphically for individual RCTs, but numerical data and statistical significance were not reported. Weight loss was similar in patients ≥65 years old compared with patients <65 years old in all dulaglutide treatment groups and was in the range of 0 to 3 kg. The incidence of documented hypoglycemia (blood glucose <70 mg/dL) was reported for individual RCTs by treatment group and category of hypoglycemia (symptomatic, asymptomatic, and nocturnal). A small percentage of patients treated with dulaglutide alone or in combination with metformin or pioglitazone reported documented symptomatic hypoglycemia (age ≥65 years old: 0–5.4%; age <65 years old: 2.7–5.6%). A higher percentage of patients treated with dulaglutide in combination with metformin and glimepiride experienced documented symptomatic hypoglycemia (age ≥65 years old: 26–35%; age <65 years old: 31–32%). The majority of patients treated with dulaglutide in combination with metformin and insulin lispro experienced symptomatic hypoglycemia (age ≥65 years old: 71–75%; age <65 years old: 80–85%), with high rates of hypoglycemia (age ≥65 years old: 29–33 events/patient/year; age <65 years old: 33–41 events/patient/year). Gastrointestinal adverse events were pooled across RCTs. Nausea was the most common event in the elderly and more likely at higher doses, but similar to patients <65 years old (age ≥65 years old: 23% at 1.5 mg vs 13% at 0.75 mg; age <65 years old: 20% at 1.5 mg vs 12% at 0.75 mg). Similar dose-dependent side effects were seen with diarrhea (age ≥65 years old: 14% at 1.5 mg vs 8.9% at 0.75 mg; age <65 years old: 12% at 1.5 mg vs 8.9% at 0.75 mg) and vomiting (age ≥65 years old: 10% at 1.5 mg vs 8.5% at 0.75 mg; age <65 years old: 10% at 1.5 mg vs 6.3% at 0.75 mg).

A retrospective pooled analysis of six RCTs (N=2,783) examined the efficacy and tolerability of once-weekly liraglutide in patients with type 2 diabetes, comparing those 65 years old and older (N=552, 20%) with those <65 years old.[2] The RCTs evaluated the effects of weekly liraglutide as monotherapy and in combination with other antihyperglycemics compared head-to-

head against other antihyperglycemics over 26 weeks. The reported outcomes included change in HbA1c, weight change, blood pressure change, and rates of hypoglycemia, nausea, vomiting, and diarrhea. Weight loss was statistically significant compared with placebo in both age groups at the 1.8 mg dose (average loss of 2.1 kg in the elderly and 1.7 kg in participants <65 years old; $P<.05$) but was not significant at the 1.2 mg dose for those ≥65 years old. No statistically significant difference in weight change was noted between the older and younger age groups. Change in systolic blood pressure compared with placebo was not statistically significant in the elderly, whereas diastolic blood pressure was significantly reduced compared with placebo, but the effect was mild (mean difference −1.47 mmHg; $P<.05$). Hypoglycemia, nausea, and diarrhea were reported, but statistical significance was not present. Hypoglycemia requiring third-party assistance was only noted in patients using concurrent sulfonylureas. Minor hypoglycemia, defined as glucose <56 mg/dL in a patient able to treat themselves, was more common at the 1.8 mg dose (15.2%) in older adults but less common at the 1.2 mg dose (4.3%) relative to placebo (9.1%). The other side effects showed a dose-dependent response. Nausea was the most common event seen in older patients (24.5% at 1.8 mg vs 20.5% at 1.2 mg vs 2% in placebo), followed by diarrhea (13% at 1.8 mg vs 13.5% at 1.2 mg vs 2% placebo) and vomiting (7.4% at 1.8 mg vs 5.4% at 1.2 mg vs 3% placebo). The incidence of gastrointestinal adverse events was not grossly different from younger patients. Of note, withdrawal of therapy because of adverse events was higher in older adults (13% at 1.8 mg, 9.7% at 1.2 mg vs 2.0% with placebo) relative to younger adults (7.6% at 1.8 mg, 7.2% at 1.2 mg vs 3.1% with placebo).

An industry-funded retrospective pooled analysis of six RCTs (N=3,188) examined the efficacy and safety of daily lixisenatide in patients with type 2 diabetes who were 65 years old or older (n=623) with those <65 years old.[3] The RCTs evaluated lixisenatide as monotherapy and in combination with other antihyperglycemics compared head-to-head against other antihyperglycemics over 24 weeks. Symptomatic hypoglycemia was defined as blood glucose <60 mg/dL or prompt symptom resolution with glucose administration. The incidence of symptomatic hypoglycemia was reported separately for each RCT and statistical significance was not assessed. Symptomatic hypoglycemia was more common when lixisenatide was combined with insulin and sulfonylureas. A small percentage of patients treated with lixisenatide alone or in combination with metformin experienced symptomatic hypoglycemia (age ≥65 years old: 0–4.7%; age <65 years old: 1.9–2.9%) compared with a larger percentage of patients treated with lixisenatide combined with sulfonylureas (age ≥65 years old: 19–22%; age <65 years old: 14–16%), and an even larger percentage of patients treated with lixisenatide combined with basal insulin (age ≥65 years old: 27–42%; age <65 years old: 28–29%) or lixisenatide combine with basal insulin and a sulfonylurea (age ≥65 years old: 53%; age <65 years old: 45%). Other reported adverse events included nausea, vomiting, diarrhea, abdominal pain, and dyspepsia. These were pooled across RCTs, but statistical significance compared with placebo or between age groups was not reported. Comparing those <65 years old versus ≥65 years old versus ≥75 years old, respectively, taking lixisenatide, nausea was present in 26% versus 29% versus 33% compared with 5.8% to 7.8% in the placebo groups, vomiting in 9.7% versus 14% versus 13% compared with 0% to 2.5% in the placebo groups, diarrhea in 8.1% versus 9.2% versus 6.3% compared with 0% to 6.5% in the placebo groups, abdominal pain in 4.1% versus 4.7% versus 2.1% compared with 0% to 3.4% in the placebo groups, and dyspepsia in 3.5% versus 6.3% versus 4.2% compared with 0% to 0.4% in the placebo groups.

CASE CONCLUSION

You agree with the patient that a GLP-1 agonist is likely to decrease her weight. You add that common side effects seen in both younger and older patients include nausea, vomiting, diarrhea, and abdominal discomfort. Hypoglycemia is not expected to be more common when combined with metformin alone but is a significant concern when combined with insulin or sulfonylureas. EBP

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Is there an increased risk for dementia in older patients receiving proton pump inhibitors?

EVIDENCE-BASED ANSWER

Use of proton pump inhibitors does not appear to be correlated to the risk of dementia in elderly patients (SOR: **B**, meta-analyses of observational studies with limitations).

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A 2019 meta-analysis of 10 studies (4 cohort, 4 case-control, 1 cross-sectional, and 1 population-based longitudinal study; N=642,305) assessed the correlation between proton pump inhibitor (PPI) use and the development of dementia or Alzheimer disease in adults.[1] Patients' average age ranged from 56 to 86 years old and percent male from 26% to 59%. Studies lasted 4 to 8 years with follow-up every 12 to 18 months. Dose and brand of PPI were not specified and methods of confirmation varied by study including pharmacy records or self-report. Diagnosis of dementia was based on DSM-IV, Cognitive Abilities Screening Instrument, and coding guidelines. PPI use was not associated with dementia (10 studies, N=642,305; hazard ratio [HR] 1.0; 95% CI, 0.9–1.2). In a subset of five studies examining the association of PPI and risk of the specific diagnosis of Alzheimer disease, no significant association was found (n=421,079; HR 0.96; 95% CI, 0.8–1.1). No evidence of publication bias was noted. Significant heterogeneity was not explained by age or sex. Limitations included exclusion of unpublished and non-English-language papers. Because many of the eligible studies were case-control studies (4 studies, n=475,272), potential selection and recall bias was present.

A 2016 cohort study (N=148) examined the possible link between PPI use and lower scores on dementia testing.[2] This study was not included in the meta-analysis because of its testing instrument. Patients were more than 65 years old, community dwelling, and did not have a previous diagnosis of dementia. Long-term PPI use was defined as more than six months of continuous use in the previous three years and based on patient report and short questionnaire. The mean age was 75 years old with over 66% female patients. Mini-mental status examination (MMSE, a 30-point screening test for cognitive impairment, where a score of 20–24 indicates mild dementia) and a clock drawing test (CDT, a visuospatial screen for dementia, scored 0–10 in this study with no threshold reported) were administered to all patients. Patients who used PPIs scored lower on the MMSE compared with control (27/30 vs 29/30; $P=.004$). Scores with the CDT were also lower in the PPI group compared with no PPI use (average 7/10 vs 8/10; $P=.02$). Long-term PPI use was associated with increased risk of dementia range score on the MMSE compared with no PPI use after controlling for history of diabetes and hypertension (24% vs 11%; odds ratio 3.7; 95% CI, 2.2–19.2; $P=.002$). Limitations included small sample size, subjective report of PPI use, and lack of adjustment for confounding factors. EBP

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Do CBT-based interventions reduce occupational stress and burnout among physicians in developed countries?

EVIDENCE-BASED ANSWER

There is a moderate improvement in work-related stress outcomes among physicians receiving cognitive behavioral therapy (CBT)-based interventions versus no interventions (SOR: **B**, meta-analysis of randomized controlled trials and controlled trials). Physicians participating in a CBT-based stress management course may demonstrate improvement in psychologic stress more than those participating in non-CBT–based interventions (SOR: **C**, nonrandomized controlled trial).

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A 2015 meta-analysis of 58 studies (54 randomized controlled trials [RCTs] and 4 controlled before-and-after studies) aimed at preventing psychological stress in 7,188 healthcare workers (5% physicians), nurses, and nursing and medical students.[1] Interventions included CBT, combined CBT with relaxation, compared with controls (no intervention or wait-listed control groups). The primary outcome was psychological stress measured by validated scales for burnout, stress, quality of life, etc. Low-quality evidence showed that CBT with or without relaxation was no different than no intervention in reducing stress symptoms at one month in healthcare workers (7 trials, n=332 [23% physicians]; standard mean difference [SMD] –0.27; 95% CI, –0.66 to 0.13). CBT with or without relaxation compared with no intervention reduced stress levels a small degree at 1 to 6 months and a moderately large degree at more than six months of follow-up (7 trials, N=549 [less than 1% physicians]; SMD –0.38; 95% CI, –0.59 to –0.16 and 2 trials, N=157 [unknown number of physicians]; SMD –1.04; 95% CI, –1.4 to –0.7). In a subgroup of only physicians, there was a moderate improvement with CBT over no intervention on any stress-related outcome at one month (2 studies, n=106; SMD –0.59; 95% CI, –1.0 to –0.18). The studies included interventions other than CBT training (ie, studies also included mental/physical relaxation and changing work schedules).

A 2004 Australian nonrandomized controlled study involving 110 general practitioner physicians (GPs) evaluated CBT for reducing stress.[2] GPs in the treatment arm (n=85) received a 5-week, 15-hour CBT stress management course while those in the control group (n=25) received a similar length, non-CBT professional development course. Physicians were incentivized by granting professional development points. Physicians were mostly between the ages of 40 and 60 years old (gender breakdown not reported) with the greatest number graduating from medical school 20 to 29 years prior (treatment group 38% vs control group 44%). Treatment group physicians were more likely to be in a group practice than those in the control group (71% vs 56%). Self-assessment outcomes scored from validated tools assessed work-related distress and general psychologic stress. The 36-point general health questionnaire, with higher scores indicating higher stress and ≥12 points set as minimum for high stress, assessed general psychological distress. The assessments were performed at baseline and at four weeks for both the treatment and the control groups. Compared with the control group, GPs in the treatment group demonstrated a 50% reduction versus a 13% increase in general psychological stress (14 points pre to 10 points post vs 12 points pre and 13 points post; $P=.001$). There was no difference between the improvements in both groups for work-related distress, work-related morale, and quality work life. Limitations of the study included lack of randomization, inequivalent comparison group numbers, and lack of reporting of gender breakdown. EBP

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Does the utilization of medical scribes reduce physician burnout in primary care settings?

EVIDENCE-BASED ANSWER

A paucity of evidence exists regarding the effects of scribe use on physician burnout in family medicine. Scribe utilization may improve physician workplace satisfaction and decrease burnout in academic outpatient internal medicine clinics (SOR: **C**, small pre-post trials).

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A 2018 three-month prospective pre-post study in an academic general internal medicine clinic assessed the impact of scribes on physician satisfaction, burnout, time spent on the electronic health record (EHR), and patient satisfaction (n=6 physicians, 1 scribe).[1] Physicians were selected based on interest and clinic schedule to allow scribe employment. A professionally trained scribe was employed full-time and worked with each physician for one session per week with remaining time divided across the faculty. Surveys were completed one week before and after the pilot. The pre-pilot 21-item and post-pilot 44-item surveys were created by the study group and included adapted questions from validated Consumer Assessment of Healthcare Physicians and Systems Clinician & Group Survey and the single-item burnout assessment. Physicians rated their burnout using a 5-point scale ranging from 1 to 5, with five reflecting the highest level of burnout and scores of greater than or equal to three indicating burnout. Patient satisfaction was categorized into "strongly agree", "agree," "neutral," "disagree," and "strongly disagree". No identified change was observed in reported burnout (1 of 6 participants reported burnout symptoms both preintervention and postintervention). Workplace satisfaction markers showed improvement from presurvey to postsurvey, namely, fewer physicians felt rushed during visits (6 vs 0), dissatisfied with clinic workflow (6 vs 2), or felt like they were spending too much time on the computer during visits (5 vs 0). More felt satisfied with overall EHR use (2 vs 4). Because of small sample size, statistical testing of significance was not performed for these measures. A decrease in physician-reported postclinic EHR documentation time was noted (mean 0.76 hours with scribe vs 1.7 hours without, $P=.02$). Patient satisfaction was not significantly affected by scribe utilization with respect to physician explanations (85% satisfied with scribe present vs 87% without, $P>.5$), time spent in room (85% vs 85%, $P>.5$), or physician computer use (83% vs 85%, $P>.5$). Limitations included small sample size, single-site, short duration, use of only one scribe, limited generalizability, and low sensitivity for burnout via one-item assessment.

A 2017 four-month prospective pre-post study in an academic general internal medicine clinic assessed the impact of clerical support on physician satisfaction, productivity, documentation timeliness, and attitudes toward clerical support staff (n=7 physicians, 1 scribe).[2] The physicians practiced part-time, together averaging 19 half-day sessions per week. The group hired support staff without formal scribe training but familiar with the EHR. The staff member assisted with order entry (laboratories, tests, imaging, and referrals), EHR documentation of previsit health maintenance, updating the medical history, and test results entry from outside facilities. Physician satisfaction was defined as quality of life (QOL) and personal balance; each was assessed with validated self-administered single-item 5-point Likert scale questions. Regarding QOL, one indicated the worst QOL and five indicated optimal QOL. Responses were categorized as good (4–5), neutral (3), and bad (1–2). Regarding personal balance, 1 indicated the least satisfaction with balance between personal and professional life and five the most satisfied. Responses were categorized as satisfied (3–5) or low satisfaction (1–2). Burnout was assessed with two questions adapted from the Maslach Burnout Inventory using a 7-point Likert scale, with one indicating "never," seven indicating "every day" and a score of five or higher (at least once a week) indicating burnout. Physician productivity was assessed by comparing current and historical work relative value units (wRVUs) for five of seven physicians

who worked in the clinic for many years. Timeliness was tracked with two subjective (5-point Likert scale) questions about when documentation was completed after hours or on weekends, with a higher score indicating more time spent documenting during those times. A focus group was conducted with all physicians two months postintervention to assess attitudes toward the new staff and workflow changes. Statistical significance was not assessed given the small sample size. Physicians reporting "good" QOL improved from 71% (5 of 7) to 100% (7 of 7). Personal balance improved from 43% (3 of 7) to 71% (5 of 7). Burnout decreased from 43% (3 of 7) to 14% (1 of 7), and feelings of callousness decreased from 14% (1 of 7) to 0% (0 of 7). wRVUs increased for four of five physicians, averaging 20.5% (range –9.2% to 27.5%). Subjective perception of timeliness improved with fewer physicians reporting incomplete documentation at clinic's end (from 100% to 57%) and fewer physicians completing notes on weekends (from 86% to 57%). Focus group discussions noted increased feelings of support, ability to focus on patient care, and decreased stress and fatigue. Physicians "ordered more preventive studies, participated more freely in other academic duties, and experienced improved patient interactions." They felt working closer with clinic staff decreased feelings of alienation and created more positive environment. Limitations included small sample size, single-site, short duration, use of only one support staff, limited generalizability, limited detection of burnout via two-item assessment only. EBP

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Does outpatient monitoring of opioid-dependent patients after release from an inpatient rehabilitation help prevent relapses/overdoses?

EVIDENCE-BASED ANSWER

Psychosocial treatment added to pharmacological treatments moderately decreases subsequent use of opiates (strength of recommendation [SOR]: **A**, meta-analysis of randomized controlled trials [RCTs] and controlled clinical trials). Both individual counseling and participation in a 12-step program after discharge from inpatient detoxification is associated with higher abstinence rates (SOR: **B**, single RCT). Time to relapse may be shorter for those who receive no formal aftercare after inpatient opioid detoxification (SOR: **C**, small observational study).

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A 2011 meta-analysis of 11 randomized controlled trials (RCTs; N=1,592) compared psychosocial and pharmacologic treatments versus pharmacologic treatment alone for opioid detoxification.[1] Patients were 67.5% male, had an average age of 35 years old, and had history of heroin use (8–11 years). Exclusion criteria included age less than 18 years old and pregnant women. The psychosocial treatments included behavioral therapy, counseling sessions (psychoeducation about detoxification misperceptions), therapeutic alliance intervention (discuss treatment goals and develop patient/counselor bond), contingency management (monetary reward for appropriate urine drug screen results), case management (access community resources), and employment and family therapy. The duration of psychosocial treatment ranged from 1 day to 12 months and the frequency of treatments ranged from daily to every two weeks. The pharmacologic treatments included methadone (starting doses 30–90 mg/d with

some tapers and some fixed doses) or buprenorphine (starting doses 4–8 mg/d with some increases in dose and some tapers). The primary outcomes were the number of patients completing the program (1 day to 12 months), use of opiates during treatment measured by intermittent urinalysis, and number of patients abstinent at follow-up (immediate to 12 months). The addition of any psychosocial treatment to any pharmacologic treatment reduced dropout rates (6 trials, N=424; relative risk [RR] 0.71; 95% CI, 0.59–0.85), use of opiates during the treatment (4 trials, N=320; RR 0.82; 95% CI, 0.7 to –0.93), use of opioids at follow-up (3 trials, N=208; RR 0.66; 95% CI, 0.53–0.82), and clinical absences during the treatment (3 trials, N=1,138; RR 0.48; 95% CI, 0.38–0.59). A key limitation of this study was the heterogeneity of the assessment of outcomes of the included studies.

A 2020 secondary analysis of a national multisite open-label RCT (n=570) examined the effects of counseling on illicit opioid abstinence rates among patients with opioid use disorder.[2] Patients were 18 years old or older (70% male, average age of 34 years old), spoke English, had opioid use disorder, and used nonprescribed opioids in the past 30 days. Participants received either extended-release naltrexone 380 mg injection every 28 days or buprenorphine-naloxone sublingual films (8–24 mg) daily. Dosing was adjusted to minimize side effects and cravings. Counseling consisted of individual counseling, group therapy, and 12-step participation occurring over a three-month period, with patients choosing frequency of sessions and reporting weekly participation via a self-reported scale. Primary outcomes were the urine toxicology results at the end of treatment and follow-up at one month and three months after treatment. A higher number of individual counseling hours was associated with lower odds of opioid continuation (greater abstinence; odds ratio [OR] 0.56; 95% CI, 0.42–0.74). Hours of 12-step participation was a lesser predictor of abstinence (OR 0.95; 95% CI, 0.92–0.98). Group therapy did not predict abstinence. Limitations included the use of a self-report scale, lack of methodological control of psychosocial interventions, and lack of long-term data.

A 2018 observational study (n=58) evaluated the effects of post-inpatient detoxification aftercare.[3] Patients (72% male, average age of 31 years old) were placed in inpatient aftercare, outpatient aftercare, or no formal aftercare groups. Outpatient aftercare lasted 12 to 24 weeks and took either an educational or a vocational approach. The primary outcome was lapse (defined as single use) or relapse (defined as return to daily use) of opioids, alcohol, benzodiazepines, cocaine, or marijuana, collected by self-report, during the last week of detox and then at three-, six-, and nine-months follow-up. Patients who opted for outpatient aftercare treatment lapsed and relapsed at a higher rate than the inpatient aftercare group; however, this was not statistically significant (hazard ratio [HR] 1.5; 95% CI, 0.75–3.1). Time to lapse or relapse was significantly shorter for patients with no formal aftercare (HR 7.7; 95% CI, 4.3–14). Limitations included possible recall bias, lack of data on the no formal aftercare group because of their high dropout rate (69% at 9 months), and lack of long-term data. EBP

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Does physician access to prescription monitoring databases reduce opioid overdose deaths?

EVIDENCE-BASED ANSWER

Prescription drug monitoring programs (PDMPs) are associated with a reduction in opioid overdose deaths (SOR: **B**, regression study). More robust PDMPs are associated with greater reductions in overdose deaths (SOR: **B**, regression study).

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A 2016 multistate (N=34) multivariate regression study examined the change in opiate overdose fatalities after the implementation of a prescription drug monitoring program (PDMP) and the features of the programs that were associated with further reductions in overdose mortalities.[1] States that implemented PDMPs during the study period of 1999 to 2013 were included with the exception of West Virginia, which was excluded because it was considered an outlier in terms of its very high rate of overdose deaths and PDMP implementation early in the study period. Opioid overdose mortality was compared in the years before and after implementation of PDMPs for each state. The multivariate model also incorporated and accounted for educational attainment, unemployment rate, and state fixed effects. The primary outcome was annual rate of opioid-related overdose deaths per 100,000 population in each state. The year following the start of a state PDMP, there were 1.1 fewer opioid-overdose deaths per 100,000 people (95% CI, –1.7 to –0.55). PDMPs with four or more drug schedules monitored and data updated weekly were associated with greater opioid death reductions (–0.55 opioid overdose–related deaths per 100,000; 95% CI, –1.02 to –0.38 and –0.82 per 100,000, 95% –1.25 to –0.38), but mandatory use/reporting did not augment the reduction (0.3 opioid overdose–related deaths per 100,000; 95% CI, –0.27 to 0.87). If a state adopted a PDMP that monitored four or more drug schedules and updated their data at least weekly, the predicted reduction in opioid deaths per 100,000 people would be 1.55. The study was limited by excluding an early adopting and outlier state (West Virginia) and inability to control for other state-specific policies that may have been implemented concurrently (ie, pill mill laws) that may have also had an effect on reducing opioid overdose deaths.

A 2017 secondary data set analysis used longitudinal panel data to examine the relationship between the strength of a state's PDMP and opioid overdose deaths.[2] The report included all 50 states and the District of Columbia between 1999 and 2014. Overall, 51 jurisdictions were analyzed over 16 1-year periods, resulting in 816 total observations. In total, 11 factors made up the composite variable for PDMP strength (possible score of 0 to 23, higher scores indicating more robust programs) with the most weight given to mandatory checking of PDMP, monitoring of more than only Schedule II drugs, and mandate to identify suspicious prescribing, dispensing, or purchasing activity. The primary outcome was age-adjusted opioid overdose death rates. The mean PDMP strength score was 5.19±5.9. Professional or licensing authorities administered 40% of PDMPs, while 32% were administered by departments of health, and 17% were administered by law enforcement agencies. Of states, 11% had access to naloxone and 8% passed good Samaritan laws. Multiple regressions were used to assess the relationship between PDMP strength score and opioid overdose death rates controlling for PDMP administration, demographic factors, and other laws that might affect opioid overdose. The model found a negative relationship between PDMP strength and overdose death. Specifically, for every one-point increase in PDMP score, opioid overdose deaths decreased by 1% (95% CI, 0.2–2). PDMPs in the first, second, and fourth quartiles were not associated with a reduction in opiate overdose death rate. However, PDMPs in the third quartile were associated with a decrease of 18% (95% CI, –34 to –1.6) for an estimated 3,300 less deaths in 2014 compared with states without PDMPs. A major limitation of the study was that the composite variable was not validated previously. This variable did not include mandatory provider participation in a PDMP, which may be an essential element of PDMP strength. EBP

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In patients with type II diabetes, is a vegan diet associated with better glycemic control compared with a conventional diabetes diet?

EVIDENCE-BASED ANSWER

A vegan diet decreases HbA1c 0.36% more than a conventional diabetes diet, and that improvement increases for those with reported high adherence to the diet (SOR: **B**, systematic reviews of small randomized controlled trials [RCTs] and conflicting small RCT).

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A 2018 systematic review of eight trials (N=424) evaluated the benefits of plant-based diet in patients with type 2 diabetes mellitus (T2DM).[1] Trials included patients 27 to 80 years old (mean of 54.8 years old), primarily in community-based settings, diagnosed with T2DM (initial HbA1c 5.5–8.3%). Any trial without baseline and postintervention HbA1c measurements for all patients was excluded. The intervention group diet was described as "vegan" or "plant-based." All studies used low-fat versions and one study allowed one serving of low-fat yogurt per day. Control group included diets from international diabetes organizations, omnivorous or conventional low-fat diet. Primary outcomes included a decrease in HbA1c of 0.55% in the intervention group compared with a mean decrease of 0.19% in the control group (no reported *P* value or timeframe given). Trials lasted 3 to 74 weeks (mean duration 23.2 weeks). Among participants with high adherence, HbA1c decreased by 0.9% within the vegan diet group compared with 0.3% for the control group, a significant between-group difference ($P=.01$). In two studies where no medication changes were made, one study showed HbA1c levels decreased 1% in the intervention group compared with 0.2% in the control group (no *P* value or timeframe given), and the other study showed HbA1c levels significantly decreased by 0.9% ($P=.002$). Limitations included small sample sizes and the inability to blind participants and participant recall bias.

A 2018 RCT (n=45) evaluated the benefits of a vegan diet compared with a portion-controlled diet in patients with T2DM.[2] Inclusion criteria were diagnosis of T2DM by laboratory or prior physician diagnosis with 6 months of hypoglycemic medications, HbA1c 6.5–10.5%, >18 years old (mean age=61 years old), ability to adhere to dietary plan, and no medication changes in previous one month. Exclusion criteria included patients already following a low-fat, vegetarian eating pattern, BMI >45 kg/m^2, alcohol misuse, use of recreational drugs in the past six months, pregnancy, signs or symptoms of acute uncontrolled diabetes, or lack of English fluency. The vegan diet and the portion-controlled diet group met weekly with a multidisciplinary team who developed an individualized diet plan and provided multi-faceted diabetes nutrition and behavior education. The vegan diet plan consisted of whole grains, vegetables, legumes, and fruits. Animal products and added oils were excluded; no restrictions were placed on energy or carbohydrate intake. The portion-controlled diet included calorie restrictions for weight loss as needed (typically a 500 calories/d deficit) and guidance on distributing carbohydrates, reducing saturated fats, favoring high-fiber foods, and limiting sodium. Medical providers were asked to avoid changing medications during the study, except in cases of medical or clinical necessity. The study lasted 20

weeks and outcomes included change in body weight, HbA1c, plasma lipids, urinary albumin, and blood pressure. No significant difference was noted in HbA1c reduction between the vegan diet and portion-controlled diet groups (median HbA1c decrease of −0.4% in both groups, $P=.68$). Limitations include small sample size, lack of blinding, and poor description of dietary adherence. EBP

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Is the introduction of allergenic foods, such as egg and peanut, to infants at 4 to 6 months of age associated with an increased risk of allergic disease later in life?

EVIDENCE-BASED ANSWER

The early introduction of egg and peanut protein at 4 to 6 months of age reduces sensitization rates in infants at high risk of allergic disease (SOR: **A**, systematic review of randomized controlled trials). The early introduction of peanut protein at age 4 to 6 months should be considered in high-risk infants (SOR: **C**, expert opinion).

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A 2016 meta-analysis of 146 randomized controlled trials (RCTs) studied the effect of early introduction of allergenic foods on the incidence of allergic or autoimmune disease.[1] Studies investigating egg introduction included infants who were 4 to 6 months old, 91% of whom were high risk for allergic disease (defined as those with eczema or egg allergy). Peanut introduction studies included patients who were 4 to 11 months old and normal or high risk for allergic disease. Exclusion criteria were variable but often included positive food allergy challenge or food sensitivity diagnosed by elevated serum immunoglobulin E levels. Control groups included placebo (most commonly rice powder) and later introduction of allergenic foods. Primary outcomes were egg or peanut allergy, which included wheeze, eczema, allergic rhinitis, food allergy, and allergic sensitization, which were diagnosed by an oral challenge test. Early egg introduction was associated with a reduction in the rate of egg allergy (5 RCTs; N=1,915; risk reduction [RR] 0.56; 95% CI, 0.36–0.87; $I^2=36\%$). Early peanut introduction likewise was associated with a reduced rate of peanut allergy (2 RCTs; N=1,550; RR 0.29; 95% CI, 0.11–0.74; $I^2=66\%$). Limitations included heterogeneity of the included studies, potential for attrition bias, and not adequately accounting for confounders such as breastfeeding rates.

A 2016 RCT (n=319) studied if the introduction of egg to infants at risk for allergy was associated with later sensitization to egg.[2] The study included four-month-old infants with a first-degree relative with allergic disease. Infants with a positive skin prick test (2 mm or more) to commercial egg white were excluded. Participants were randomized to receive daily whole-egg powder from 4 to

8 months old versus the control group who were limited to an egg-free diet during the intervention period. Diets of both groups were then liberalized at eight months. The primary outcome was the proportion of infants sensitized to egg whites on skin prick test at 12 months. Early introduction of egg was associated with a reduced odds of egg sensitization compared with placebo (11% versus 20%; odds ratio 0.46; 95% CI, 8.2–18.9; number needed to treat=11). Limitations included small study size and the middle to high socioeconomic status of subjects that reduced generalizability.

In a 2019 clinical report, the American Academy of Pediatrics (AAP), with support from the National Institute of Allergy and Infectious Diseases, recommended the purposeful early introduction of peanut protein in high-risk infants 4 to 6 months old to prevent peanut allergies (based on the 2016 meta-analysis above).[3] No evidence-based recommendations for peanut protein introduction were made for infants at low or no risk. The AAP concluded the ideal timing and health benefit of early egg introduction was still unclear due to significant differences between studies of the exposed populations and the dosing and formulation of the egg introduced. EBP

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Does face-to-face parental counseling and patient education increase vaccination rates in children and adolescents?

EVIDENCE-BASED ANSWER

Face-to-face parental education with a healthcare professional leads to a small improvement in rates of pediatric vaccination. Similarly, education measures likely result in small increase in parental knowledge about pediatric vaccination (SOR: **A**, systematic review and meta-analysis of randomized controlled trials). Face-to-face education of low-income families through community-based organizations may result in a moderate increase in influenza vaccination rates and overall rates of vaccine-complete children (SOR: **B**, single prospective intervention study).

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A 2018 Cochrane systematic review of 10 randomized controlled trials (RCTs; N=4,527) aimed to answer whether face-to-face interventions delivered to parents improved knowledge and beliefs about vaccinations, intention to vaccinate, and children's vaccination status.[1] Investigators evaluated three studies from low- or middle-income countries and seven studies from high-income countries. Patient demographics varied widely. Some studies included both male and female patients, whereas others included only female patients. For many studies, the age range was not specified further than "infants" or "school-aged" children. Study interventions included face-to-face dialogue, oral presentations, individual or group classes or seminars, and home outreach sessions. Study controls included phone-only communication, usual care, or no intervention. Low-certainty evidence from seven studies found that face-to-face communication resulted in increased receipt of vaccines (N=3,004, relative risk 1.20; 95% CI, 1.04–1.37). Four studies (N=657) measured

parental knowledge of vaccines, vaccine-preventable diseases, contraindications to vaccination, or a combination using varying scales. Evaluations administered via questionnaire or face-to-face interview at three or six months postintervention suggested that face-to-face information probably improved parent knowledge, with the intervention group scoring 0.19 SDs higher than control group (95% CI, 0.00–0.38). The review was limited by the inconsistency in study design and statistical heterogeneity.

A 2011 prospective intervention study of 1,531 children younger than 19 years old in Onondaga County (New York state) examined vaccination rates before and after face-to-face parental vaccine education.[2] Participants included only families with income less than 150% of the federal poverty level. Pediatric infectious disease specialists provided education during a Salvation Army holiday gift distribution event. Investigators identified incompletely vaccinated children using the New York State vaccine registry; children not vaccinated against seasonal influenza were offered the flu vaccine after an approximate 10-minute education session, which addressed parental vaccine concerns, provided education on vaccine importance, and reviewed the pediatric immunization schedule with relevant vaccine information sheets. Investigators reviewed the state vaccine registry every 4 to 6 weeks for the subsequent nine months and measured rates of vaccine-complete children at nine months postintervention. Additionally, rates of childhood influenza vaccination were compared with influenza vaccine rates observed in all children in Onondaga County. Among children enrolled in the study, 1,477 had accurate vaccination records at registration, with 28% considered vaccine-complete. Influenza vaccination rates increased from 32% to 49% (mean difference 17%; 95% CI, 15.5–19.5). The most significant improvement occurred in the 0 to 3-year-old cohort, with an absolute increase of 25% (95% CI, 21.2–29.8). This compared with an 8% increase among all children in the county (95% CI, 7.4–8.1) and 5% statewide (95% CI, 4.7–4.8). Study limitations included a lack of proper comparison and control groups to assess efficacy of face-to-face education on vaccination rates other than the flu vaccine. EBP

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Does vaccinating children with the varicella vaccine increase the incidence of shingles in the adult population?

EVIDENCE-BASED ANSWER

Unclear. Across national cohorts, implementation of universal varicella vaccination in children does not consistently demonstrate an increase in the incidence of shingles in adult populations. Small increases in the rates of shingles are noted in certain age groups (SOR: **C**, based on conflicting evidence from a systematic review of population studies and 2 retrospective single cohort studies).

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A 2019 systematic review and meta-analysis (n=undefined) of 12 population-based studies from six countries (Australia, Taiwan, Spain, the United States, Canada, and Germany) evaluated the impact of varicella vaccination on the incidence of herpes zoster (HZ) over time.[1] All study populations implemented widespread varicella vaccination in children 11 months old and older, in either one or two doses, and reported the incidence of

chickenpox and HZ before and after introduction of widespread vaccination. Compared with the period before widespread introduction of the varicella vaccine, one German study found that implementation of widespread vaccine led to a small but significant increase of confirmed hospitalized cases of HZ in patients 10 to 49 years old (+0.29 cases/100,000 people; 95% CI, 0.18–0.39 cases/100,000 people) but did not increase for people 50 years old or older (+0.02 cases/100,000 people; 95% CI, –0.39 to 0.43 cases/100,000 people). Pooling data from two population in the United States and Taiwan investigators noted an increasing trend in HZ diagnoses before universal vaccine implementation when adjusted for age (+0.38 cases/1,000 persons, $P<.001$) and a nonsignificant decrease after implementation (–0.08 cases/1,000 persons, $P=.41$).This negative trend was significant in people 40 to 49 years old (–0.44 cases/1,000 people; 95% CI, –0.52 to –0.37 cases/1,000 people).

A 2020 retrospective cohort study examined the age-related incidence of HZ and annual rates of change over three separate periods with differing varicella vaccine policies.[2] Data were gathered from administrative claims filed in the Truven Health MarketScan Commercial Database and Medicare Supplemental Database from January 1991 to December 2016. All persons with at least one calendar year of enrollment from 1996 to 2016 were included. Data were grouped over three separate periods: 1991 to 1995 before universal childhood vaccination was adopted, 1995 to 2006 when the one-dose vaccination was used, and 2007 to 2016 during which time the 2-dose vaccination was standard. Incidence of HZ was calculated for each year of the study and by age groups 0 to 17, 18 to 34, 35 to 44, 45 to 54, 55 to 64, and 65 years old and older based on reporting of the first medical claim with the corresponding International Classification of Diseases code as primary or secondary diagnosis. Based on graphical data, the incidence of HZ in patients 18 years old and older increased from 1991 to 2012 with a plateau in levels from 2013 to 2016. In the 65-year-old and older group, the rate of increase was found to slow significantly from 12.4% to 3.6% to 1.7% across the three periods ($P<.05$). Based on boxplot images, the rate of increased incidence in the 18- to 34-year-old group and in the 55- to 64-year-old groups also slowed between the second and third periods. While the 35- to 54-year-old group demonstrated a consistent but nonsignificant rise in rates across all three periods. Multiple limitations were noted as data were only reported for individuals who sought medical care, varicella vaccination status could not be determined, and it was unclear if those with HZ had a primary or recurrent outbreak. Authors also noted that the incidence rates for the prevaccine period may not have been reliable because of the fact that MarketScan data were unavailable, so enrollment was estimated.

A 2018 retrospective cohort study evaluated the effect of universal varicella vaccination on HZ epidemiology.[3] Data were collected by the Miyazaki Dermatologist Society from 1997 to 2017 of all new medically documented HZ cases in 43 clinics in the Miyazaki prefecture, Japan. The incidence of HZ was compared in age groups >60 years old, <60 years old, and 20 to 49 years old based on population statistics and reported in 1,000 person-years to determine which generation was most affected. Universal varicella vaccination was introduced in Japan in October 2014. The incidence of HZ increased significantly after introduction of universal vaccination compared with time before for those less than 60 years old (2,614 vs 2,410 person-years, $P<.05$) and for those 60 years old or older (3,914 vs 1,833 person-years, $P<.05$). The increase, compared with the time before vaccination, in HZ incidence in the total population studied was most significant during 2014 to 2015 (odds ratio [OR] 1.08; 95% CI, 1.04–1.12) and 2015 to 2016 (OR 1.07; 95% CI, 1.03–1.10). EBP

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of herpes zoster in the child-rearing generation as its short-term effect. *J Dermatol Sci*. 2018;92(1):89-96. [STEP 3]

In pediatric patients, what role does palatal petechiae have in the diagnosis of GAS pharyngitis?

EVIDENCE-BASED ANSWER

Although the physical examination finding of palatal petechiae is more specific than tonsillar exudates and tender cervical lymph nodes for ruling in group A streptococcus (GAS) pharyngitis, this diagnostic finding alone is insufficient to rule in or rule out the disease and should be used in conjunction with additional signs and symptoms of GAS (SOR: **B**, systematic review of case–control and retrospective cohorts and single prospective study).

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A 2011 systematic review of 34 case–control and retrospective studies (N=24,418) assessed the efficacy of using palatal petechiae for children and adolescents aged 3 to 18 years old as a clinical marker for strep pharyngitis.[1] Patients with original medical data on history, physical examinations, or with a documented positive throat culture were included; those with only rapid antigen testing data were excluded. Those who presented to clinic (27 studies) or emergency department (7 studies) and had signs or symptoms of streptococcal pharyngitis who tested positive for group A streptococcus (GAS) on culture were compared with those who tested negative. The symptoms assessed for accuracy of diagnosis were sore throat plus the presence of scarlatiniform rash, palatal petechiae, pharyngeal exudates, vomiting, and tender cervical lymph nodes. The assumed prevalence of GAS among those children presenting with sore throat was 37%, and clinical signs were evaluated via positive likelihood ratio (LR+) and negative likelihood ratios (LR–). Palatal petechiae was a small but helpful contributor to diagnosing GAS (LR+ 2.7; 95% CI, 1.9–3.8) but was not helpful in ruling out GAS (LR– 0.90; 95% CI, 0.86–0.94). Scarlatiniform rash was better than palatal petechiae for ruling in the disease (LR+ 3.91; 95% CI, 2.00–7.62) but was just as poor for ruling out the disease (LR– 0.94; 95% CI, 0.90–0.97). Pharyngeal exudates, vomiting, and tender cervical nodes all had less powerful likelihood ratios when compared with palatal findings or scarlatiniform rash. Review limitations included lack of specificity regarding how signs and symptoms were defined or elicited in the original articles and the reference standard used was positive throat culture instead of antistreptococcal serology, which is unable to differentiate true infection from the carrier state and likely underestimated the accuracy of signs and symptoms.

A 2016 prospective, nonrandomized observational study (n=100) evaluated whether the addition of palatal petechiae to the Centor criteria improved accuracy of clinical diagnosis of acute strep pharyngitis in children and adolescents 4 to 17 years old.[2] All patients presented with complaints of sore throat and were examined clinically using the Centor criteria (fever, anterior cervical lymphadenopathy, tonsillar exudate, and absence of cough) as well as the presence of palatal petechiae, abdominal pain, and rash. Those who tested positive with a rapid strep test confirmed with throat culture were compared with those without positive laboratory tests. All 100 patients had sore throat, fever, and erythema of tonsils. Of the 100 patients, 86 had no cough, 85 had tender anterior cervical lymph nodes, 20 had tonsillar exudates, and 8 had palatal petechiae. Only 16 of 100 patients (16%) had a positive rapid strep test and only nine of 16 patients (56%) had a positive throat culture. Children with palatal petechiae were significantly more likely to have a positive throat culture for strep compared with those with tonsillar exudates (75% vs 35%, $P<.0001$). EBP

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In couples with infertility, is natural procreative technology successful in achieving live birth?

EVIDENCE-BASED ANSWER

Natural procreative technology treatment over a 24-month period was found effective in producing live births in 53% to 63% of couples with infertility issues (SOR: **C**, consistent results from 2 case series). Comparison of natural procreative technology to other methods of treating infertility is problematic because of substantial variability of infertility treatments and outcome data.

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A 2008 case series of 1,072 couples in Ireland assessed the efficacy of natural procreative technology on couples experiencing infertility.[1] Women included had a mean age of 36 years old and a prior mean time of attempted conception of 5.6 years before enrollment. Additionally, 24% reported a previous live birth and 33% had already received assisted reproductive technology (ART). Natural procreative technology provided to couples included instructions on timing of intercourse around ovulation. The female partner may also receive vitamin B6 and guaifenesin to enhance cervical mucus quality, clomiphene, human chorionic gonadotropin, or progesterone. The male partner received standard treatment of male infertility. Couples were also taught the Creighton Model FertilityCare System, a method of cervical mucus and menstruation charting. Surgical treatments were not used in this study. The primary outcome measured was live births achieved within 24 months after initiating treatment. Accounting for all study participants, the rate of successful live birth after conception within 24 months of treatment was 26% and life-table analysis, where withdrawal or continuing treatment at the end of study are excluded, was 53%. Notably, 5% of couples conceived with Creighton Model FertilityCare System tracking and timed intercourse alone. Qualitative assessment by the authors concluded that benefits of natural procreative technology included increased access, decreased cost, fewer multiple births, and reduced invasiveness. Head-to-head trials are lacking, but the authors concluded the rates achieved here are comparative to more invasive treatments observed in other studies.

A newer but much smaller 2012 retrospective case series of 108 infertile couples in Canada measured the effectiveness of natural procreative technology by tracking live birth rates.[2] Women included had a mean age of 35 years old and a prior mean time of attempted conception of 3.2 years before enrollment. ART had previously been used for some couples including 22% who received previous intrauterine insemination and 8% who received previous in vitro fertilization. A portion of couples (20%) reported a previous live birth with or without ART. Teaching couples the Creighton Model FertilityCare System and natural procreative technology interventions were similar to those described above with the addition of amoxicillin, erythromycin, and clarithromycin to enhance cervical mucus quality and surgical treatments including laparoscopy when necessary. The primary outcome of live births was assessed for 24 months after initiating treatment. After 24 months, the crude live birth rate was 38%. After removing those who withdrew or ceased treatment before full completion, the live birth rate was 66%. EBP

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What are the most effective oral medications for ovulation induction in women with PCOS?

EVIDENCE-BASED ANSWER

The aromatase inhibitor letrozole leads to a significantly higher live birth rate when treating women with subfertility related to polycystic ovarian syndrome when compared with other common oral agents including clomiphene citrate and metformin (SOR: **A**, meta-analysis or randomized controlled trials [RCTs]). No difference was noted in the rate of multiple gestation or ovarian hyperstimulation syndrome when using letrozole compared with clomiphene citrate (SOR: **A**, meta-analysis of RCTs).

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A 2019 Cochrane review of 41 randomized controlled trials (RCTs; N=4,552) examined the use of metformin in women from 25 to 33 years old with polycystic ovarian syndrome (PCOS)-related subfertility compared with clomiphene citrate.[1] Dosages of metformin ranged from 850 to 2,000 mg per day, with the most common regimen being 500 mg three times per day. Clomiphene citrate doses ranged from 50 to 150 mg daily, given cycle days 2 through 7. Most studies followed patients for 3 to 6 months. Metformin compared with placebo improved the live birth rate overall (4 trials, N=435 women; odds ratio [OR] 1.6; 95% CI, 1–2.5; low-quality evidence). Metformin compared with clomiphene citrate did not improve the live birth rate (5 trials, N=741; OR 0.71; 95% CI, 0.49–1.0; very low-quality evidence). The combination of metformin with clomiphene citrate compared with placebo alone did not improve the live birth rate either (10 trials, N=1,219; OR 1.3; 95% CI, 0.98–1.7; low-quality evidence). Subgroup analysis of patients by body mass index showed a possible increase in live birth rates among nonobese patients who used metformin compared with clomiphene citrate alone (3 trials, N=241; OR 1.7; 95% CI, 1.0–2.94; very low-quality evidence). When comparing metformin with placebo, no difference was noted in miscarriage risk or multiple gestation pregnancy rates; however, analysis was limited by low numbers, poor quality of the studies, and heterogeneity of the data overall.

In 2018, a Cochrane systemic review of 42 RCTs (7,935 women) examined effectiveness and safety of the aromatase inhibitor letrozole in the treatment of subfertile women with PCOS-related ovulation dysfunction.[2] All patients were women 18 to 40 years old, diagnosed with PCOS-related anovulation and treated with letrozole 2.5 to 7.5 mg per day orally for five days compared with clomiphene citrate 50 to 150 mg per day orally for five days followed by timed intercourse or intrauterine insemination. Thirteen of these studies compared letrozole with clomiphene citrate with adjuncts such as metformin (1,000–1,500 mg daily). Letrozole compared with clomiphene citrate achieved higher live birth rates regardless of the use of additional adjuvants (13 trials, N=2,954; OR 1.7; 95% CI, 1.4–2.0; number need to treat=10; moderate-quality evidence). Letrozole compared with clomiphene citrate did not change miscarriage rate (18 trials, N=1,210; OR 0.94; 95% CI, 0.70–1.3; high-quality evidence), multiple gestation pregnancy rates (17 trials, N=3,579; OR 0.69; 95% CI, 0.41–1.2; high-quality evidence), or ovarian hyperstimulation syndrome of 0.5% in both groups. Although the review also investigated difference in letrozole compared with placebo, selective estrogen receptor modulators, and anastrozole, authors were unable to make conclusions because of the limited number of studies. EBP

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

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For medication management of early pregnancy loss, what are the advantages of misoprostol with mifepristone compared with misoprostol alone?

EVIDENCE-BASED ANSWER

In women with missed abortion, misoprostol with mifepristone is likely superior to misoprostol alone for complete expulsion of products of conception (SOR: **B**, inconsistent evidence based on meta-analyses of multiple randomized controlled trials [RCTs] and individual RCTs). The highest quality RCT available found a higher complete expulsion rate for misoprostol with mifepristone (84%) compared with misoprostol alone (67%), as well as a reduced need for uterine aspiration. The most commonly used dose is misoprostol 800 μg vaginally and mifepristone 200 mg orally. Misoprostol with mifepristone compared with misoprostol alone also decreases the risk of vomiting, nausea, and fever (SOR: **A**, based on a meta-analysis of RCTs).

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A 2019 meta-analysis of five randomized controlled trials (RCTs) (N=676) directly compared misoprostol with and without mifepristone for the treatment of missed abortions.[1] The trials included women with a spontaneous loss of a nonviable intrauterine pregnancy 0 to 14 weeks gestation meeting criteria for missed abortion or blighted ovum. Women with incomplete or inevitable abortion or other pretreatment vaginal bleeding were excluded. Intervention protocols varied among the studies. In general, the participants were treated with either a single dose of misoprostol (400–800 μg vaginal route [PV] oral route [PO]) or a single dose of mifepristone 200 mg (3 trials) or 600 mg (2 trials) followed by a misoprostol 400 to 800 μg PV (4 trials) or 400 μg PO (1 trial) starting 24 to 48 hours later. All trials included the option for subsequent misoprostol doses (minimum 1 additional dose, maximum 5 additional doses) of misoprostol 400 to 800 μg PV (4 trials) or 400 μg PO (1 trial) based on protocol or symptoms after initial misoprostol dose (interval assessments at minimum 2 hours, maximum 72 hours). After misoprostol administration was complete, three trials followed up at 24 to 72 hours to assess efficacy and bleeding, one trial was performed in-hospital therefore patients were continuously monitored though endpoint was not delineated, and one trial did not clarify immediate follow-up but performed a questionnaire at 14 days. The primary outcome was the rate of complete evacuation of products of conception; secondary outcomes were complications of treatment. The rate of complete evacuation did not differ between treatment regimens (risk ratio [RR] 1.2; 95% CI, 0.98–1.5). Misoprostol with mifepristone was associated with lower risk of some side effects compared with misoprostol alone, including fever (RR 0.33; 95% CI, 0.19–0.57), nausea (RR 0.42; 95% CI, 0.24–0.72), and vomiting (RR 0.55; 95% CI, 0.32–0.94). The overall quality of included studies was assessed as moderate by the authors because of lack of blinding, allocation concealment, attrition, and detection bias.

The largest and highest quality RCT (n=300) included in the meta-analysis above compared PO mifepristone plus PV misoprostol with PV misoprostol alone for the management of a missed abortion.[2] Patients were 18 years old or older with a closed cervix and documented nonviable intrauterine pregnancy at gestational age 5 to 12 weeks confirmed by ultrasound, who chose medical management over expectant management or uterine aspiration. Primary outcomes were the expulsion rate of the gestational sac by 30 days and the rate of uterine aspiration. The treatment group was given PO mifepristone 200 mg under direct observation by investigator then given misoprostol 800 μg to insert PV 24 hours later at home. The control group was given PV misoprostol 800 μg to insert at home, and no oral placebo was

given. Participants returned 1 to 4 days after misoprostol use for evaluation, including ultrasound, by an investigator blinded to intervention. If the gestational sac was not expelled at the time of evaluation, patients were offered expectant management, a second dose of misoprostol, or uterine aspiration. Patients were followed for 30 days after randomization by phone interview. At 30 days, misoprostol with mifepristone compared with misoprostol alone resulted in a higher complete expulsion rate (84% vs 67%; RR 1.3; 95% CI, 1.1–1.4; number needed to treat [NNT]=6) and a lower rate of need for uterine aspiration (8.8% vs 23.5%; RR 0.37; 95% CI, 0.2–0.7; NNT=7). Combination therapy resulted in an increased risk of vomiting compared with misoprostol alone (27% vs 15%; RR 1.8; 95% CI, 1.1–2.8; NNH=9). Study validity was limited by lack of blinding of the patients.

In 2018, the updated American College of Obstetrics & Gynecology Practice Bulletin on Early Pregnancy Loss recommended PO mifepristone 200 mg 24 hours before PV misoprostol 800 μg to improve treatment efficacy (Level of Recommendation A, based on good and consistent scientific evidence from multiple RCTs and primarily references the Schreiber 2018 RCT as best available evidence).[3] The ACOG bulletin noted that REMS restrictions (Risk Evaluation and Mitigation Strategy by the U.S. Food and Drug Administration) in effect posed an unnecessary barrier to accessing this medication in routine practice, and ACOG advocated for lifting such restrictions. EBP

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Do group prenatal visits increase the likelihood of breastfeeding versus individual prenatal visits?

EVIDENCE-BASED ANSWER

The overall effect of group prenatal care on breastfeeding rates is not certain. Centering pregnancy group prenatal care increases the rates of breastfeeding initiation at hospital discharge in women compared with individual prenatal care (SOR: **B**, meta-analysis of randomized controlled trials [RCTs] and cohort studies). However, group prenatal visits compared with standard care do not change breastfeeding rates from immediately to 3 months postpartum (SOR: **B**, meta-analyses of RCTs and cohort studies).

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A 2018 meta-analysis of seven studies (2 RCTs, 4 cohort studies, and 1 mixed-methods study) analyzed the effect of centering pregnancy (CP) versus individual prenatal care on a variety of perinatal outcomes.[1] CP is standardized model of group prenatal care with two-hour sessions, providing interaction between a group of patients, their obstetrical provider, and a facilitator. Supplemental feeding was permitted. The primary outcome was breastfeeding initiation at time of discharge among 8,041 patients. Patients were women with varying risk status, racial composition, age (range 16–26 years old), and 94% were low income. CP was initiated in the second trimester in all studies. Authors excluded studies without African-American women in population sample or that did not include breastfeeding as an outcome. The CP intervention consisted of groups of 8 to 10 meeting every two weeks for 10 to 12 weeks beginning in the second trimester. Standard CP programs include two breast feeding educational sessions.

Individual prenatal care served as the control. CP patients were more likely to initiate breastfeeding compared with those receiving individual care (7 studies; N=8,041; odds ratio [OR], 1.5; 95% CI, 1.3–1.8). In a subgroup analysis with only African-American patients, CP increased breastfeeding initiation over individual care by 71% (4 studies; N=1,458; OR, 1.7; 95% CI, 1.3–2.3).

A 2016 meta-analysis of 14 trials (4 RCTs and 10 observational cohort studies) evaluated the effect of group prenatal care versus standard individual care on the primary outcome of preterm birth and secondary outcomes of birth weight, neonatal intensive care unit (NICU) admission, and breastfeeding initiation (N=10,321).[2] Five studies overlap with the previous meta-analysis. Patients included adolescent and adult (11 years old and above) women enrolled in prenatal care (group vs standard individual care) in a variety of settings in the United States, Iran, or Canada. Study intervention included CP (as defined above) or group prenatal care (not further defined) compared with standard individual care. Breastfeeding initiation was defined as ranging from immediately postpartum to breastfeeding at three months postpartum. Seven studies evaluated breastfeeding outcomes (7 trials with 4 overlapping from the previous meta-analysis). No difference was found in breastfeeding initiation between women receiving group versus standard individual care (7 studies; N=7,386; relative risk [RR], 1.1; 95% CI, 0.99–1.2, I^2=93%). No significant differences was found between group and standard individual care in the rate of preterm birth or NICU admissions (11 studies; N=8,863; RR, 0.87; 95% CI, 0.7–1.1 and 7 studies; N=7,365; RR, 0.91; 95% CI, 0.68–1.2). There was a decreased rate of low birth weight infants in the group prenatal care (9 studies; N=8,802; RR, 0.81; 95% CI, 0.69–0.96). A key limitation of this review meta-analysis was design heterogeneity of included studies. EBP

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Are herbal supplements safe and effective for increasing breastmilk supply?

EVIDENCE-BASED ANSWER

For many herbals, we do not have much data. A combination herbal tea of fenugreek, ginger, and turmeric may increase breastmilk supply and does not demonstrate adverse effects (SOR: **C**, small randomized controlled trial [RCT]). Consumption of Mother's Milk tea has not demonstrated maternal or infant adverse effects (SOR: **C**, small RCT) but may not be more effective than lemon verbena control. A variety of other herbal galactagogues have demonstrated positive effects on breastmilk volume and infant weight gain (SOR=**C**, systemic review of small trials).

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A 2018 Taiwanese randomized controlled trial (RCT) evaluated the effect of an herbal combination compared with placebo on milk volume and nutrient content in exclusively breastfeeding mothers, 20 to 40 years old, at one-month postpartum (singleton birth, n=50).[1] The intervention group took three capsules (each containing fenugreek seed 200 mg, ginger 120 mg, and turmeric 100 mg), three times a day for four weeks. The control group took a matched placebo. Mean two-day breastmilk volume (mL/d, measured by manual pump) and breastmilk nutritional content were measured at baseline and two- and four-week post-intervention. Breastfeeding mothers receiving supplementation had increased milk volume over baseline compared with the control arm at two weeks (increase

TABLE. Systematic review of galactagogues on breastfeeding outcomes[3]

Outcome	Intervention vs comparison	N	Outcomes	P
Breast milk volume	Torbangun soup vs fenugreek capsules vs moloco + B-12 tablets	75	Day 28 Increase in mean breastmilk volume from baseline: 479 mL (65%) vs 400 mL (25%) vs 385 mL (10%)	< .05
	Drug X vs ergometrine	82	Day 4 breastmilk volume: 277 vs 155 g Day 6 breastmilk volume: 414 vs 293 g	< .05
	Milk thistle vs placebo	50	Day 30 mean breastmilk volume 990 vs 650 g	< .01
	Humana/still tea (containing fenugreek) vs apple tea (placebo) vs no intervention (control)	66	Mean breastmilk volume: 73.2 vs 38.8 vs 31.1 mL	< .05
Infant weight gain	Shatavari mixture (2 tsp daily of 100 g, 15% shatavari) vs placebo	64	Median infant weight gain: 30 vs 26 g/d	NS
	Shatavari capsules vs placebo	60	Mean percent increase in infant weight: 16.1% vs 5.7%	< .05

NS=not significant "reported as comparable".

of 49% vs 11%; $P=.003$) and at four weeks (increase of 103% vs 24%; $P<.001$). No differences were observed in milk calories, macronutrients, or vitamin, calcium, or iron content. No differences were found in adverse effects. No patients were lost to follow-up. This study may be underpowered to detect rare adverse events.

A 2018 RCT of exclusively breastfeeding women 18 to 45 years old without identified milk production issues evaluated adverse effects of Mother's Milk tea, infant growth, and maternal perception of infant satisfaction with feeds at two-week to three-month postpartum (singleton birth, n=60).[2] One bag of Mother's Milk tea contains 560 mg bitter fennel fruit, 350 mg anise fruit, 210 mg coriander fruit, 35 mg fenugreek seed, 35 mg blessed thistle herb, and flavoring botanicals including lemon verbena. Women consumed 3 to 5 cups per day of either Mother's Milk tea or matched placebo of lemon verbena tea. In-person assessments at two and four weeks included validated scales of maternal quality of life and breastfeeding self-efficacy, breast engorgement (Likert scale of 0–10), infant satisfaction with feeds (Likert scale of 0–5), adverse effects, and infant growth. Additional phone visits every three months for one year inquired about adverse effects. No difference was found between the groups in maternal or infant adverse effects. There was only a self-reported increase in breastmilk production. This study was limited by self-reported data and risk for reporting bias. The study population was predominantly white and college educated. It excluded women with poor milk supply and did not assess infant latch. This study was funded and supplies provided by the Mother's Milk tea parent corporation.

A 2013 systematic review of six RCTs (N=397) assessed effects of various purported herbal galactogogues (shatavari, torbangun, milk thistle, moloco, fenugreek, and Drug X [a Japanese combination of 16 herbs]) on various breastfeeding outcomes (**TABLE**).[3] No meta-analysis was performed because of the heterogeneity of study interventions and outcomes. EBP

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Is progestin-only contraception associated with higher incidence of postpartum depression?

EVIDENCE-BASED ANSWER

Probably not. Although progestin-only contraception is associated more frequently with postpartum depression in adverse reporting data, trial data demonstrate no association and some studies have shown a protective effect (SOR: **B**, systematic review and a retrospective cohort study with inconsistent results).

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A 2019 systematic review (4 studies, N=76,409) evaluated the association between postpartum progestin contraceptive use and postpartum depression.[1] Patients included postpartum women within one year of delivery without a history of depression before delivery. Intervention groups received progestin-only contraceptives, which included progestin-only pills, injectable contraception, or progestin-containing long-acting reversible contraception (intrauterine devices or implants). Control groups included placebo or no hormonal contraception. The primary outcome was the risk of developing postpartum depression, defined by a positive depression scale or a depression diagnosis in report claims data measured between six weeks and 12 months after delivery. Standard depression scales included the Edinburgh Postnatal Depression Scale, Beck Depression Inventory, or the Montgomery-Asberg Depression Rating Scale. In the largest included retrospective cohort study (n=75,528), etonogestrel implant use was not associated with an increased risk of depression at one year postpartum when compared with controls (adjusted hazard ratio [aHR] 1.0; 95% CI, 0.83–1.2). Both levonorgestrel intrauterine devices (IUDs) and progestin-only pills were associated with a decreased risk of postpartum depression when compared with controls (levonorgestrel IUD aHR 0.65; 95% CI, 0.52–0.82; progestin-only pills aHR 0.56; 95% CI, 0.49–0.64). An included randomized controlled trial (RCT; n=242) and retrospective cohort study (n=247) found no difference in depression incidence between injectable depot medroxyprogesterone compared with nonhormonal contraception users. One RCT (n=180) found no increased risk of major or minor depression with injectable norethisterone enanthate (not available in the United States) compared with placebo at three-month follow-up using the Edinburgh Postnatal Depression Scale (relative risk 1.2; $P=.57$). Limitations included short follow-up periods, and potential generalizability concerns given the largest study involved a military population (98.8% of systematic review patients).

A 2017 retrospective cohort study (N=6,157,897) analyzed the association between postpartum depression and hormonal contraception.[2] Data were collected from the U.S. Food and Drug Administration Adverse Event Reporting System database between 2004 and 2015. Postpartum depression cases were defined based on report terminology from the Medical Dictionary of Regulatory Activities, and only reports with a medication categorized as a "primary suspect" for the adverse event were included. In the reporting period, 253 cases of postpartum depression were identified. Levonorgestrel IUD, etonogestrel implant, and drospirenone-containing contraceptive pills were associated with reports of postpartum depression. Odds ratios (ORs) were calculated using a disproportionality analysis. The levonorgestrel IUD, etonogestrel implant, and drospirenone pill were associated with the development of postpartum depression (levonorgestrel IUD OR 13; 95% CI, 8.7–18; etonogestrel implant OR 14; 95% CI, 8.5–23; drospirenone OR 5.4; 95% CI, 2.7–11). Limitations included the use of a database of reported symptoms rather than standardized depression scales, and timing of contraceptive administration was not reported, so temporality or causality could not be demonstrated. EBP

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In sepsis, is the use of balanced crystalloids better than unbalanced crystalloids in decreasing mortality?

EVIDENCE-BASED ANSWER

Yes. The use of balanced crystalloids for fluid resuscitation during sepsis results in an absolute 4.9% decrease in 30-day in-hospital mortality (SOR: **B**, randomized crossover trial). Treatment with balanced crystalloids is not associated with an increase in length of stay or cost per day (SOR: **B**, retrospective cohort study).

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A 2017 nonblinded, cluster-randomized, multiple crossover trial suggested that balanced crystalloids improved clinical outcomes in critically ill adults (Isotonic Solutions and Major Adverse Renal Events Trials [SMART] trial). In 2019, a secondary analysis of the SMART trial investigated whether the use of balanced crystalloids versus normal saline decreased mortality in critically ill adults diagnosed with sepsis (n=1,641).[1] Patients were adults admitted to the medical intensive care unit (ICU) whom had an International Classification of Diseases 10 (ICD-10) code for sepsis identified within the first five billing codes for their hospitalization. Median age of study participants was 60 years old, with 55% of these participants being male and 75% being Caucasian. In total, 824 participants received balanced crystalloids (lactated ringers or Plasma-Lyte A) for fluid resuscitation versus 817 whom received usual therapy with unbalanced crystalloids (normal saline). The primary outcome was 30-day in-hospital mortality. Secondary outcome measures included ICU-free days, ventilator-free days, vasopressor-free days, renal replacement therapy–free days, all-cause mortality, and major adverse kidney events within 30 days. The use of balanced crystalloids resulted in a lower rate of 30-day in-hospital mortality (adjusted OR [aOR] 0.74; 95% CI, 0.59–0.93) with an absolute risk reduction of 4.9% (26.3% vs 31.2%). Patients who received balanced crystalloids also experienced more ventilator-free days (27 vs 26 days, aOR 1.4; 95% CI, 1.1–1.7) and fewer adverse events (292 vs 328 events, aOR 0.78; 95% CI, 0.63–0.97). No clinically significant improvement was noted in ICU-free days, vasopressor-free days, or renal replacement therapy–free days. No harm was identified with the use of balanced crystalloids. Study limitations included a lack of blinding of fluid group assignments, completion of the study within a single academic center, the use of ICD-10 codes as a surrogate for clinical assessment, and the increased risk for type I error (because of secondary analysis of a clinical trial from a single site).

A 2015 retrospective cohort study that included administrative and financial data collected from 360 hospitals within a US healthcare alliance investigated whether the type(s) of IV fluids used during the initial resuscitation of patients with severe sepsis impacted in-hospital mortality (n=60,734).[2] Patients were 18 years old or older and admitted on a nonelective basis to a medical ICU with a primary or secondary diagnosis of sepsis. All patients had blood cultures collected and received vasopressors, antibiotics, and ≥2 L of crystalloid fluids within the first 48 hours of admission. Patients who had undergone major surgical procedures or who were transferred between

medical facilities were excluded. Four exposure categories were identified based on the type(s) of IV fluids administered within the first 48 hours: isotonic saline, saline combined with balanced crystalloids (lactated ringers), saline combined with balanced crystalloids and colloids, or saline combined with colloids (albumin). The primary outcome was hospital mortality occurring during the index hospitalization, with secondary outcome measures evaluating hospital length of stay and costs per day among survivors.

The mortality rate for patients receiving isotonic saline was 20.2% (95% CI, 19.5–20.9). The addition of balanced crystalloids decreased this to 17.7% (95% CI, 16.4–18.9). Saline combined with balanced crystalloids and colloids resulted in a morality rate of 19.2% (95% CI, 17.0–21.4). The use of saline combined with colloids was associated with an increase in the mortality rate to 24.2% (95% CI, 22.9–25.4). Propensity score matching confirmed that patients receiving balanced crystalloids had lower mortality rates than those who received isotonic saline and colloids (relative risk [RR] 0.84; 95% CI, 0.76–0.92) or isotonic saline alone (RR 0.78; 95% CI, 0.70–0.89). No significant differences were noted in length of stay and costs per day between patients receiving and not receiving balanced crystalloids. No adverse effects were reported from the use of balanced crystalloid, but this study was limited by the fact that patients received fluid combinations as opposed to only one type of IV fluid. In addition, significant differences in treatment group characteristics, comorbidities, and total fluid volumes administered served as confounding variables. EBP

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In patients with acute mania, which antimanic medication regimen is the most effective treatment?

EVIDENCE-BASED ANSWER

In adult patients experiencing acute mania, antipsychotics, mood stabilizers, and combinations of antipsychotics and mood stabilizers are all effective in reducing mania symptoms, with combination therapy associated with the greatest improvements (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). When monotherapy is used for acute mania, atypical antipsychotics, especially risperidone and olanzapine, are generally more effective and better tolerated than other agents (SOR: **A**, network meta-analysis of RCTs).

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A 2015 meta-analysis of 62 randomized controlled trials (RCTs; N=15,177) assessed the efficacy and acceptability of antipsychotics, mood stabilizers, and combination treatment for managing symptoms of acute mania in adults.[1] All patients had acute mixed or manic episodes based on Diagnostic and Statistical Manual of the American Psychiatric Association, Volume IV (DSM-IV) criteria. Treatments evaluated included antipsychotic monotherapy (50 trials), mood stabilizer monotherapy (44 trials), and combination therapy (16 trials) with treatment duration ranging from 2 to 6 weeks. Mood stabilizers included lithium, valproate, and carbamazepine. Antipsychotics included aripiprazole, asenapine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Specific dosing information was not provided. Because of the heterogeneity among included trials, results were pooled and converted into a standardized mean difference (SMD) for efficacy. Acceptability was assessed using dropout rates via odds ratios (ORs). All three treatments relieved symptoms compared with placebo. Combination therapy was significantly more effective than mood stabilizers (SMD –0.28; 95% CI, –0.40 to –0.17) and was equally as effective as antipsychotic monotherapy (SMD –0.14;

TABLE. Improvement in mania symptoms of various medications compared with placebo[2]

Treatment	No. of trials	N	Dosing ranges/info	Standardized mean difference (95% CI)
Aripiprazole	6	1,419	15–30 mg/d	0.4 (0.2 to 0.6)[a]
Asenapine	2	569	18.2 mg/d	0.3 (0.1 to 0.6)[a]
Carbamazepine	2	427	643–756 mg/d	0.4 (0.2 to 0.6)[a]
Cariprazine	4	1,198	3–12 mg/d	0.5 (0.2 to 0.7)[a]
Haloperidol	5	549	2–30 mg/d	0.5 (0.4 to 0.7)[a]
Lamotrigine	2	330	25–200 mg/d	0.1 (–0.2 to 0.4)
Licarbazepine	1	313	1,000–2,000 mg/d	0.1 (–0.3 to 0.5)
Lithium	7	1,214	900–1,500 mg/d or 0.7–1.3 mEq/L	0.5 (0.3 to 0.6)[a]
Olanzapine	6	1,335	5–20 mg/d	0.5 (0.3 to 0.6)[a]
Paliperidone	4	967	3–12 mg/d	0.4 (0.1 to 0.7)[a]
Quetiapine	4	1,007	100–800 mg/d	0.4 (0.1 to 0.6)[a]
Risperidone	3	823	1–6 mg/d	0.7 (0.4 to 0.9)[a]
Tamoxifen	2	74	20–140 mg/d	2.9 (2.4 to 3.5)[a]
Topiramate	4	1,074	200–600 mg/d	0.1 (–0.2 to 0.3)[a]
Valproate	5	1,046	500–3,057 mg/d	0.3 (0.2 to 0.5)[a]
Verapamil	1	20	480 mg/d	–0.1 (–1.0 to 1.0)
Ziprasidone	3	663	116–164 mg/d	1.3 (0.1 to 0.6)[a]

[a] Statistically significant.

95% CI, –0.29 to 0.02). Both monotherapies were similar in effectiveness compared with each other. Compared with placebo, antipsychotics (OR 0.6; 95% CI, 0.5–0.7), mood stabilizers (OR 0.8; 95% CI, 0.7–1.0), and combination therapy (OR 0.7; 95% CI, 0.5–0.98) all had significantly lower dropout rates. Antipsychotics had significantly fewer dropouts than mood stabilizers (OR 0.8; 95% CI, 0.6–0.9).

A 2015 network meta-analysis of 57 RCTs (N=14,256) measured the effectiveness and discontinuation of antimanic treatments in acute bipolar disorder.[2] Patients (mean age 39 years old) were all diagnosed with bipolar 1 manic or mixed state according to the DSM-IV criteria. Those with bipolar 2, schizoaffective disorders, or bipolar not specified were excluded. Intention-to-treat datasets were used whenever available, and 99% of studies were double blinded. A variety of different antipsychotics were measured and compared with placebo (see **TABLE**). Manic symptom improvement was again measured by pooled SMDs. Secondary outcomes measured were response rates (at least a 50% reduction of baseline mania scores) and all-cause discontinuation rates. Various medications relieved symptoms significantly compared with placebo (see **TABLE**), with risperidone and olanzapine performing the strongest. Head-to-head comparisons showed similar results between treatments except for risperidone being significantly more effective compared with both aripiprazole (SMD 0.3; 95% CI, 0.01–0.5) and valproate (SMD 0.3; 95% CI, 0.1–0.6). Olanzapine was associated with significantly lower short-term discontinuation rates when compared with haloperidol (OR 0.6; 95% CI, 0.4–0.9), asenapine (OR 0.5; 95% CI, 0.3–0.9), lithium (OR 0.5; 95% CI, 0.3–0.7), and cariprazine (OR 0.5; 95% CI, 0.3–0.8). A key limitation of the analysis was the inclusion of only monotherapy management, despite the common practice of using more than one agent in the setting of acute mania and lack of clear demographic data other than age, which makes generalizing data difficult. EBP

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In patients presenting with skin and soft tissue infections, is the Laboratory Risk Indicator for Necrotizing Fasciitis score useful for ruling out necrotizing fasciitis?

EVIDENCE-BASED ANSWER

No. Although a high Laboratory Risk Indicator for Necrotizing Fasciitis score increases the chances that a patient has necrotizing fasciitis, a low score should not be used to exclude the diagnosis in patients presenting with soft tissue infections (SOR: **B**, based on meta-analysis of cohort and case-control studies, and a prospective observational cohort).

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A 2019 meta-analysis evaluated the accuracy of physical examination, imaging, and Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score in the diagnosis of adults with soft tissue infection.[1] The analysis included 23 trials (N=5,982; 16 retrospective cohort studies, 5 prospective cohort studies, and 2 retrospective case-control studies). The trials included patients 16 years old or older in whom necrotizing infection was suspected. Evaluations were conducted in the emergency department, hospital wards, or intensive care unit and included at least one of the following: physical examination, imaging modalities, or LRINEC score. Diagnosis was confirmed by surgical findings, histopathology, or death from suspected necrotizing infection. LRINEC scores were calculated from a composite of points assigned to each of six laboratory serum values: C-reactive protein, white blood cell count, hemoglobin, sodium, creatinine, and glucose (see **Table**). For a diagnosis of necrotizing fasciitis, a LRINEC score greater than or equal to six had a sensitivity of 68% (14 trials, N=4,330; 95% CI, 0.51–0.81), a specificity of 85% (95% CI, 0.76–0.91), a positive likelihood ratio (LR+) of 4.5, and a negative likelihood ratio (LR−) of 0.38. For LRINEC scores greater than or equal to eight, sensitivity was 41% (9 trials, N=1,905; 95% CI, 0.29–0.54), specificity of 95% (95% CI, 0.90–0.98), LR+ of 8, and LR− of 0.62. Limitations of this analysis derived from the quality and heterogeneity of the individual trials and their design.

A 2020 prospective observational study (n=931) evaluated the performance of LRINEC score in the diagnosis of necrotizing fasciitis.[2] From April 2015 to December 2016, the study enrolled patients 18 years old or older who were admitted through the emergency department with a diagnosis of necrotizing fasciitis or

TABLE. Laboratory Risk Index for Necrotizing Fasciitis[1]

Variable	Result	Score
C-reactive protein (mg/dL)	<15 ≥15	0 +4
White blood cell count ($\times 10^3/\mu L$)	<15 15-25 >25	0 +1 +2
Hemoglobin (g/dL)	>13.5 11-13.5 <11	0 +1 +2
Sodium (mEq/L)	≥135 <135	0 +2
Creatinine (mg/dL)	≤1.6 >1.6	0 +2
Glucose (mg/dL)	≤180 >180	0 +1

severe cellulitis of the extremities. Patients were excluded if they had lesions involving the trunk or neck, or if they had previously received antibiotics or wound debridement. Study endpoint was hospital discharge. Patients were further excluded from the study if they were discharged in less than 48 hours or if infection was mild enough to be treated with oral antibiotics before 48 hours. Necrotizing fasciitis was confirmed by operative findings and histopathology. Severe cellulitis was presumed where parenteral antibiotics were required for greater than 48 hours or when an abscess requiring debridement was present. A total of 825 patients met the criteria for severe cellulitis and 106 had pathology-proven necrotizing fasciitis.

A LRINEC score was calculated for all patients included in the study with LRINEC scores greater than or equal to six having a sensitivity of 43% (95% CI, 0.34–0.53), a specificity of 83% (95% CI, 0.80–0.86), LR+ of 2.5, and LR− of 0.69. For LRINEC scores greater than or equal to eight, sensitivity decreased to 27% (95% CI, 0.19–0.37), specificity increased to 93% (95% CI, 0.91–0.94), with LR+ of 3.9 and LR− was 0.78. LRINEC showed poor performance with area under the receiver-operating characteristic curve for accuracy of 0.7 (95% CI, 0.64–0.75). This single-center study lacked confirmatory testing for severe cellulitis and limited evaluation to the extremities, reducing its generalizability. EBP

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Is a serotonin–norepinephrine reuptake inhibitor superior to an SSRI in the treatment of major depressive disorder in adults?

EVIDENCE-BASED ANSWER

No, serotonin–norepinephrine reuptake inhibitors (SNRIs) are not consistently clinically superior to SSRIs in treating major depressive disorder (MDD). SNRIs, such as duloxetine, have a statistically but not clinically significant higher discontinuation rate than SSRIs, such as escitalopram, because of adverse drug reactions (SOR: **A**, consistent results from 2 meta-analyses of randomized controlled trials [RCTs]).

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A 2010 meta-analysis of 15 RCTs (N=3,094) compared the efficacy and potential adverse reactions of SSRIs and SNRIs in the treatment of MDD.[1] Patients were 18 years old or older and met MDD diagnosis by scoring at least 15 on the Hamilton Depression Rating Scale for Depression (HAM-D) or at least 18 on the Montgomery-Asberg Depression Rating Scale (MADRS). Patients had a one-to-two-week washout period or were antidepressant naive, and then received 8 to 12 weeks of an oral SNRI or SSRI in therapeutic doses. SSRIs evaluated included escitalopram (3 trials), fluoxetine (5 trials), paroxetine (4 trials), and sertraline (3 trials), and SNRIs included duloxetine (5 trials) and venlafaxine (10 trials). Medication doses varied between studies but remained within recommended therapeutic ranges for each medication. Targeted outcome data were assessed at study end and included the number of patients who achieved

symptom remission (defined as a score of less than 9 on the HAM-D or less than 12 on the MADRS) and the number of patients who withdrew because of lack of efficacy or adverse drug reactions. Clinical significance was defined as at least a 10% difference between treatment groups for remission and dropout rates. After pooling of all 15 trials, SNRIs demonstrated statistically but not clinically significant higher remission rates than SSRIs (49% vs 42%, $P=.007$). Because of known literature of escitalopram being more effective than other SSRIs, a sub-analysis was conducted of 12 pooled trials that did not include escitalopram. The sub-analysis (12 trials, N=2,934) did increase the difference in remission rates between SNRIs and SSRIs from 5.7% to 7.5% ($P=.002$) but still failed to achieve at least a 10% difference. Dropout rates because of lack of efficacy were similar between groups.

A 2018 meta-analysis of three RCTs (N=1,120) compared the efficacy and tolerability of duloxetine with escitalopram in the treatment of MDD.[2] Patients were adults with MDD diagnosed using Diagnostic and Statistical Manual version IV or IV-TR criteria, and all had a score of 22 or higher on the MADRS. All patients were treated with an eight-week regimen of either 10 to 20 mg escitalopram or 60 to 120 mg duloxetine. Outcomes measures included remission, defined as a MADRS score of less than or equal to 10 or a HAM-D score of less than or equal to seven, and discontinuation rates because of any cause including adverse drug reactions. No significant difference was noted between escitalopram and duloxetine in pooled remission rates by both HAM-D (3 RCTs, N=1,078, relative risk [RR] 1.0; 95% CI, 0.83–1.23) and MARDS (2 RCTs, N=549, RR 1.1; 95% CI, 0.94–1.38). Escitalopram had a lower discontinuation rate because of adverse drug reactions than duloxetine (RR=0.47; 95% CI, 0.25–0.90, $I^2=51\%$). Among the three studies, no significant difference was noted in the pooled overall discontinuation rates of escitalopram and duloxetine; however, significant heterogeneity was noted ($I^2=63\%$). EBP

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Does omega-3 supplementation improve dry eye symptoms?

EVIDENCE-BASED ANSWER

Omega-3 fatty acids may have some beneficial effect on dry eye symptoms, but the magnitude of that effect is unclear (SOR: **C**, conflicting meta-analyses).

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A 2019 systematic review of 34 randomized controlled trials (RCTs; N=4,314) from 13 countries examined the effect of omega-3 and omega-6 fatty acid supplementation for treatment of dry eye disease.[1] Four trials (N=677) specifically examining omega-3 supplementation versus placebo or no treatment were identified. Two trials included patients with moderate-to-severe dry eye, one trial included only mild disease, and one trial did not specify. Patients were of all ages and had dry eye diagnoses as defined by the trial investigators. Doses of omega-3s ranged between 600 and 3,000 mg of a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) taken orally daily. The source of omega-3s was variable. The primary outcome was difference in Ocular Surface Disease Index (OSDI), a measurement of dry eye symptomatology. The minimally clinically important difference for OSDI is

considered 4.5 to 7.3 units for mild-to-moderate dry eye disease and 7.3 to 13.4 for moderate-to-severe dry eye disease. Outcomes were measured between 1 and 12 months. No significant improvement in OSDI scoring was noted for the omega-3 supplementation group compared with placebo (mean difference [MD] –2.5 units; 95% CI, –5.1 to 0.2 units). Another subgroup analysis (N=70) of two trials compared omega-3 supplementation added to conventional therapy versus conventional therapy alone after one and three months of treatment. Mean pretreatment OSDI scores were in the moderate to severity range. Conventional therapy consisted of once-daily eyelid hygiene plus a once-daily lipid emulsion drop in one trial and artificial tears every four hours and betamethasone 0.1% drops every eight hours in the other trial. Statistically significant but borderline clinical symptom improvement was noted in the omega-3 group plus conventional therapy compared with conventional therapy alone (MD –7.2 units; 95% CI, –14.0 to –0.2 units).

A 2019 meta-analysis of 17 RCTs (N=3,363) measured the efficacy of omega-3 fatty acid supplementation versus placebo in the treatment of dry eye disease of varying severity and etiology.[2] The majority of studies were conducted in India and the United States. The EPA dose ranged between 127.5 and 2,000 mg and DHA dose ranged between 99 and 1,000 mg given daily. Mean follow-up occurred at 1 to 12 months. Because of variable reporting methods, results were pooled and converted into a standardized MD (SMD). After pooling of all 17 trials, reductions in dry eye symptom scoring were strongly, significantly higher in the omega-3 supplementation group compared with placebo (SMD 0.97; 95% CI, 0.55–1.4; I^2=96%).

The largest multicenter, double-blind RCT (n=535) to date comparing 3,000 mg of omega-3 supplementation versus placebo included in both reviews above was extended to evaluate effects of discontinuing omega-3 supplements compared with placebo after the study's initial 12-month phase.[3] Patients who completed the initial study's 12-month follow-up visit and who were assigned to the omega-3 treatment arm of the trial were eligible to participate. Of the original participants, 43 participants chose to participate in the extension study. The extension study population was similar to the original RCT with mean age of 58 years old. Patients were then randomized to either receive an additional 12 months of omega-3 supplementation or placebo. No significant difference in OSDI scores was noted between the two groups (MD –0.6 units; 95% CI, –11.0 to 9.5 units) after 12 months. EBP

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Do serial ECGs improve the evaluation of ACS?

EVIDENCE-BASED ANSWER

Not much. The addition of serial electrocardiograms (ECGs) does not improve the diagnosis of acute coronary syndrome (ACS) compared with routine chest pain protocols or troponin levels (SOR: **B**, 2 prospective cohort studies). However, serial ECGs with persistent ischemia improve long-term prediction of myocardial infarction and mortality (SOR: **B**, prospective cohort). Current guidelines recommend serial ECGs in the evaluation of ACS when the initial ECG is nondiagnostic (SOR: **C**, expert opinion).

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A 2018 prospective cohort study of 365 adult patients presenting to the emergency department (ED) with undifferentiated chest pain examined whether the addition of serial electrocardiograms (ECGs) to routine care improved the prediction of major adverse cardiac events or acute coronary syndrome (ACS) at 30 days.[1]

Hemodynamically stable adult patients (mean age 53 years old) who presented with symptoms concerning for ACS received routine care and up to two serial ECGs at 30- to 90-minute intervals. Patients with evidence of ST-elevation myocardial infarction (MI) or ventricular arrhythmia on initial ECG were excluded. Routine care included serial troponin measurements and Thrombolysis in Myocardial Infarction (TIMI) scoring. TIMI is a validated, 7-point risk score used to assess risk of major adverse cardiac events in patients presenting with undifferentiated chest pain; scores of 0 to 1 are generally accepted as low risk and scores of two or more are accepted as intermediate to high risk. Overall prevalence of major adverse cardiac events (defined as a composite endpoint of all-cause mortality, MI, or coronary revascularization) was 6.9%. Positive serial ECG changes did not improve prediction of major adverse cardiac events or ACS at 30 days when added to the use of routine care, TIMI scores of 2 plus, or troponin measurement (net reclassification improvement –0.03; 95% CI, –0.07 to 0.06).

A 2005 prospective cohort study of 706 patients admitted to a chest pain unit evaluated which elements of their chest pain protocol, including use of serial ECGs, were most useful in the diagnosis of ACS at presentation.[2] Adult patients with a mean age of 54 years old presenting to the ED with chest pain were admitted to the chest pain unit if they had a normal or nondiagnostic initial ECG. Routine care included serial ECGs and ST segment monitoring, serial cardiac biomarkers, and, if appropriate, exercise stress testing. ACS was diagnosed in 8.5% of patients based on troponin values (60 of 706 patients). For the diagnosis of ACS with myocyte necrosis or clinical MI on presentation, serial ECGs and ST segment monitoring performed significantly worse than all other tests with no overlapping CIs (positive likelihood ratio [LR+] 5.4; 95% CI, 3.0–9.8), whereas troponin T≥0.03 ng/mL performed best (LR+ 282; 95% CI, 70–1,126). Serial ECGs and ST segment monitoring also performed significantly worse than all other tests except initial creatine kinase-MB at ruling out ACS (negative likelihood ratio [LR–] 0.8; 95% CI, 0.70–0.92). Troponin T≥0.03 ng/mL again performed best (LR– 0.10; 95% CI, 0.05–0.22).

A 2020 prospective cohort study evaluated the long-term predictive value of serial ECGs on 1,675 patients who presented to a single-center ED with chest pain.[3] Adult patients with a mean age of 65 years old who presented to the emergency department with chest pain had two ECGs taken three hours apart. Patients were grouped based on ECG findings: those with no ischemic signs on initial or second ECG (n=1,321), those with ischemic signs on the first ECG that later resolved (n=92), those with ischemic signs on only the second ECG (n=25), or those with ischemic signs on both (n=237). Patients were followed for two years with the endpoints being all-cause mortality, acute MI, and revascularization. A total of 172 events occurred between 30 days and 2-year follow-up; events occurring within 30 days were excluded. Patients with consistent ischemic ECG changes had significantly higher risk for an event occurring compared with those with no ischemic findings (adjusted hazard ratio 1.47; 95% CI, 1.01–2.13). No increased risk for an event was noted in those with only a second ECG positive finding and those with a resolved ischemic ECG compared with the non-ischemic ECG group.

A 2010 American Heart Association consensus guideline recommended serial ECGs or continuous 12-lead ST-segment monitoring for low-risk patients presenting with chest pain and clinical suspicion for ACS (no strength of recommendation).[4] Serial ECGs at 5- to 10-minute intervals or continuous 12-lead ST-segment monitoring was recommended if the initial ECG was nondiagnostic but the patient remained symptomatic, and high clinical suspicion was noted for ST-elevation MI. EBP

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Does a plant-based diet lower cardiovascular risk in adults?

EVIDENCE-BASED ANSWER

Yes. A healthy plant-based diet is associated with a 19% to 25% reduction in cardiovascular disease incidence and mortality (SOR: **A**, meta-analysis of cohort studies and 2 additional cohort studies with consistent results). However, eating a solely plant-based diet consisting of unhealthy foods is not protective against cardiovascular disease (SOR: **B**, cohort studies).

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A 2017 meta-analysis of eight cohort studies (N=81,138) compared the incidence of cardiovascular disease in vegetarians to omnivores.[1] The studies included adults in the United States, United Kingdom, and Germany with ages ranging from 37 to 57 years old. A vegetarian diet was defined as a diet excluding meat and meat products, poultry, seafood, and flesh from any animal. The comparison was an omnivorous diet defined as consumption of all types of food including meat and meat products, poultry, seafood, and flesh from any animal. Primary outcomes included the combination of incidence and mortality from ischemic heart disease or cardiovascular disease more broadly over 5 to 21 years of follow-up. The vegetarian diet group was not significantly different from the omnivore group in the combination of incidence and mortality from cardiovascular disease (5 studies; N=47,757; relative risk [RR] 0.93; 95% CI, 0.86–1.0), but the vegetarian diet was associated with a reduced risk of incidence and mortality from ischemic heart disease (7 studies; N=65,058; RR=0.75; 95% CI, 0.68–0.82). This study is limited by the biases inherent to cohort studies, including the lack of randomization and the inability to assess for causation.

A 2017 cohort study (N=209,298) examined the association between a plant-based diet and cardiovascular disease.[2] The cohort population included female registered nurses and male health professionals, 25 to 75 years old. Participants were excluded if they had coronary heart disease, cancer, stroke, coronary artery surgery, or reported implausible daily calories (extremely low or extremely high). The data from food frequency questionnaires was analyzed to create a plant-based index, assigning positive scores to plant foods and negative scores to animal foods. Additionally, they created a healthy plant-based diet index with the highest scores for healthy plant foods (ie, whole grains, fruits, or vegetables) and lower scores for unhealthy plant food group (ie, juices, sweetened beverages, refined grains, or potatoes/fries) and animal-based foods. Finally, they created an unhealthy plant-based diet index that assigned higher scores for unhealthy plant-based foods and lower scores for healthy plant-based foods and animal-based foods. The primary outcome was nonfatal myocardial infarction or fatal coronary heart disease, self-reported by participants during biennial questionnaires with blinded review of medical records by study physicians to confirm diagnoses. Higher scores in the healthy plant-based index were associated with a reduction in cardiovascular disease (hazard ratio [HR] 0.75; 95% CI, 0.68–0.83) compared with lower scores in the healthy plant-based index. Higher scores in the unhealthy plant-based diet index were associated with an increased risk of cardiovascular disease (HR 1.32; 95% CI, 1.20–1.46) compared with lower scores. The study was limited by potential confounders of smoking and other comorbidities (ie, diabetes), which were more common in the unhealthy plant-based food group and potential bias resulting from self-reported data.

A 2019 cohort study (N=12,168) examined the association between a plant-based diet and cardiovascular disease.[3] The studied population included adults 45 to 64 years old without cardiovascular disease, history of myocardial infarction, heart or arterial surgery, heart failure, stroke, or cancer at baseline. The cohort was followed for 21 years with data collected from the Atherosclerosis Risk in Communities study. The participants' diets were classified using four diet indices: overall plant-based diet index, provegetarian diet index, healthy plant-based diet index, and unhealthy plant-based diet index. All plant foods received higher

scores in the index and animal foods received lower scores based on a similar scoring system as the previous study. Each cohort was divided into quintiles based on the indices, which were compared based on the primary outcomes, including cardiovascular disease and death from cardiovascular disease. Those in the highest quintile for healthy plant-based diet index had a lower risk of cardiovascular disease mortality compared with the lowest quintile (HR 0.81; 95% CI, 0.68–0.97). Limitations included potential bias resulting from self-reporting of diet. EBP

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For patients with heart failure, does remote monitoring of vital signs prevent hospital admissions?

EVIDENCE-BASED ANSWER

Telemonitoring (use of home vital monitoring devices and telephone-supported care) of heart failure (HF) patients reduces HF-related hospital admissions but does not reduce all-cause hospital admissions (SOR: **A**, meta-analysis of randomized controlled trials [RCTs] and single large RCT).

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A 2017 meta-analysis of 39 randomized controlled trials (RCTs; N=11,758) evaluated remote monitoring of vital signs and telecommunication for patients with heart failure (HF).[1] Patients were mean ages of 43 to 83 years old and 31% to 100% males. Follow-up periods ranged from 90 days to 3 years. Patients were hospitalized with New York Heart Association Functional Classification I-IV HF, predominately with impaired left ventricular ejection fraction (LVEF <40% or 50%) with one study with preserved left ventricular function (LVEF≥40%). All patients received "optimized medical therapy," including treatment with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker and a β-blocker. The control group (n=5,823) received usual care according to standard guidelines. The intervention group (n=5,935) received telemedicine support (teletransmission or telephone support) along with usual care. Teletransmission included home vital monitoring devices that transmitted heart rate, blood pressure, oxygen saturation, and weight. The primary outcomes were reduction in all-cause and HF-related admission rates, length of stay, and mortality. All-cause hospital admissions were similar between the telemedicine group and the control group (27 trials, N=8,577; pooled odds ratio [OR] 0.92; 95% CI, 0.82–1.04; I^2=71), but telemonitoring produced a significant reduction in HF-related admissions (29 trials, N=8,055; pooled OR 0.63; 95% CI, 0.53–0.76; I^2=77%). All-cause mortality and HF-related mortality were reduced in the combined telemedicine group compared with the control group (30 trials, N=9,979; pooled OR 0.8; 95% CI, 0.71–0.91; I^2=34% and 8 trials, N=2,281; pooled OR 0.69; 95% CI, 0.55–0.86). No harms were reported. Publication bias was detected in the analysis of the HF-related hospital admission rate.

A 2016 multicenter RCT (n=1,437) evaluated telemonitoring of patients with HF after hospitalization compared with usual care.[2] Patients were 50 years old or above (mean age 73 years old), 46% female, with mean ejection fraction of 43%, currently admitted to the hospital, and being actively treated for HF. Patients were excluded if they had dementia, if they weighed over 204 kg, lacked a usable phone, resided in a skilled nursing facility, were on chronic hemodialysis, had an organ transplant in the past or pending, or had a planned intervention intended to correct a HF-related underlying condition. The intervention group (n=715) received predischarge education, scheduled telephone calls, symptom tracking, and daily home remote vitals monitoring using electronic equipment with automated transmission (weight scale, blood pressure, and heart rate monitor linked to a device). The control group (n=722) was provided "usual care" with education before hospital discharge and a follow-up call. The primary outcome was 180-day all-cause readmission, and secondary outcomes included 30-day all cause-readmission, 30-day mortality, and 180-day mortality. The 180-day all-cause readmission rate of patients was not significantly different for the intervention group compared with the control group (51% vs 49%; adjusted hazard ratio 1.03; 95% CI, 0.88–1.20). No difference was noted in secondary outcomes of 30-day all-cause readmission, and 30-day or 180-day all-cause mortality between the two groups. No adverse events were reported. Thirty-day mortality rates were underpowered. Patient adherence (defined as participation in at least 50% of planned monitoring activities) to the intervention was poor with 61% telephone call and 55% telemonitoring adherence. EBP

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Does the addition of exercise to caloric restriction increase weight loss in adults compared with caloric restriction alone?

EVIDENCE-BASED ANSWER

Exercise compared with diet alone adds modest weight loss at six months but is no different at 12 months (SOR: **A**, 2 randomized controlled trials [RCTs]). The addition of exercise lowers waist circumference (by 1–2.5 cm), preserves lean body mass, and may reduce body fat (SOR: **B**, RCTs with heterogeneous outcomes).

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A 2012 randomized controlled trial (RCT) compared calorie-restricted diet, exercise, and combination diet and exercise to no intervention on weight loss in 439 postmenopausal sedentary women.[1] Patients, mean age 58 years old with mean body mass index (BMI) 31 kg/m^2 and 48% average body fat, who exercised less than 100 minutes per week at moderate intensity or greater were included. The study excluded patients with recent use of hormone therapy, diabetes, breast cancer history, consumption of more than two alcoholic drinks per day, tobacco use, abnormal exercise stress test, or recent use of a weight loss program or medication. A control group (n=87) was instructed not to change exercise or diet for 12 months. The calorie-restricted diet group (n=118) received a 1,200 to 2,000 kcal/d diet with less than 30% fat, intensive dietician and group support, food journals,

and weekly weigh-ins to measure adherence. The exercise group (n=117) exercised at moderate to vigorous intensity ≥45 minutes five d/wk for 12 months. An exercise physiologist supervised three sessions per week and used activity logs to measure adherence. The diet and exercise group (n=117) received both interventions. Study statistical significance was set at $P=.0083$. After 12 months, no difference in mean weight loss was noted in the diet and exercise versus the diet-alone groups (–8.9 kg/–10.8% vs –7.2 kg/–8.5%, $P=.02$). However, diet and exercise significantly lowered waist circumference (–7 vs –4.5 cm, $P=.004$) and body fat percentage (–5.9% vs –4.2%, $P<.0001$) compared with diet alone. Limitations included a majority non-Hispanic White college graduate patients and exclusion of important health conditions seen in many older female patients.

A 2011 RCT compared diet, exercise, and diet plus exercise on physical performance, weight loss, and body composition in 107 older adults with obesity.[2] At baseline, patients in the diet and diet plus exercise groups were on average 70 years old, BMI of 37 kg/m^2, 9% and 12% men, and average weight 104 and 99 kg, respectively. All patients had a sedentary lifestyle, and mild-to-moderate frailty, defined using a modified physical performance test, difficulty in instrumental activities of daily living (ADL) or ADL, or a reduced VO_{2peak} on a treadmill examination. Exclusion criteria were history of severe cardiopulmonary disease; cancer; musculoskeletal or neuromuscular impairment; visual, hearing, or cognitive impairments; current smoking; or medications affecting bone health or metabolism. The control group (n=27) received monthly general advice on a healthy diet. The diet group (n=26) received a 500 to 750 kcal energy deficit diet with 1 g/kg protein daily to achieve 10% weight loss at six months and weekly food log review with dietician counseling. The exercise group (n=26) exercised 90 minutes three days per week including aerobic exercise, resistance training, flexibility, and balance. The diet and exercise group (n=28) received both interventions. Average weight loss was not different between the diet and exercise and diet groups (–8.6 kg/–9% vs –9.7 kg/–10%, $P=.67$) at 12-month follow-up, but lean body mass decreased less in diet and exercise group than diet group (–1.8 kg/–3% vs –3.2 kg/–5%, $P=.04$). Body fat was not statistically different between the groups (–6.3 kg/16% vs –7.1 kg/17%, $P=.57$). This study was limited by its sample size and thus did not have enough power to detect a difference in secondary outcomes.

A 2010 single-blind RCT compared calorie-restricted diet with increased physical activity for 12 months (initial activity, n=67) to the identical dietary intervention with increased physical activity delayed after six months (delayed- activity, n=63) on weight in 130 adults with BMI ≥35 kg/m^2.[3] Baseline values for patients in the initial group and delayed group were age 46 and 48 years old, BMI 44 kg/m^2, weight 121 and 117 kg, 10% and 5% men, respectively. Exclusion criteria were recent weight loss ≥5%, participation in a weight loss program in the past year, bariatric surgery history, uncontrolled diabetes or hypertension, coronary artery disease, cancer within five years, or pregnancy within six months. All patients received a reduced energy diet of 1,200–2,100 kcal/d with approximately 50% carbohydrate, 25% protein, 25% fat, some free meal replacements, and food logs for adherence tracking. The activity prescription included moderate-intensity activity, similar in intensity to brisk walking, increasing by 10-minute increments to 60 minutes five days per week, with activity logs and intermittent wearable tracking for adherence. Both groups received 3 to 4 groups or individual contacts per month. At six months, the initial-activity group lost more weight than the delayed-activity group (–11 kg; 95% CI, –9.1 to –13 vs –8.2 kg; 95% CI, –6.4 to –9.9; $P=.02$), had a lower waist circumference (115.8 cm; 95% CI, 112.8–118.8 cm; vs 116.5 cm; 95% CI, 113.5–119.5 cm; $P=.01$), and less body fat (51.7 kg; 95% CI, 48.0–54.5 kg; vs 53.3 kg; 95% CI, 50.3–56.3; $P=.008$). At 12 months, no difference was noted in weight loss, waist circumference, or body fat. The study was limited by a small number of male patients but did include 37% African American participants. EBP

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Is platelet-rich plasma injection more effective at improving pain than corticosteroid injection in chronic lateral epicondylitis?

EVIDENCE-BASED ANSWER

Platelet-rich plasma (PRP) injection is more effective than corticosteroid injection in reducing lateral epicondylitis pain in long-term follow-up (>2 months; SOR: **A**, meta-analysis of randomized controlled trials [RCTs] and 1 RCT with consistent results). In the short-term (<2 months), PRP and corticosteroid injection seem to be similar in effect (SOR: **B**, meta-analysis and 1 RCT with inconsistent results).

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A 2019 meta-analysis compared platelet-rich plasma (PRP) injection and corticosteroid injection for the treatment of lateral epicondylitis pain.[1] Patients were adults, 18 years old or older, with mean ages ranging from 33 to 47 years old. Mean duration of symptoms was greater than six months in two trials and not reported in the remaining studies. The meta-analysis did not report how the diagnosis of lateral epicondylitis was made or any additional inclusion or exclusion criteria. PRP was prepared by collecting the patient's own blood and spinning it once or twice such that serum with a high concentration of platelets and platelet-derived growth factors was collected. PRP injection volume ranged from 1 to 3 mL with or without local anesthetic (bupivacaine or xylocaine). Corticosteroids included 1 mL of triamcinolone 40 mg/mL with bupivacaine, or 2 mL of 40 mg/mL methylprednisolone with or without xylocaine. Injection methods, number of injections, and duration of treatment were not described. The primary outcome was pain as documented by a visual analog scale (VAS, 0 to 10 scale), and follow-up ranging from 4 weeks to 1 year. At long-term follow-up (>2 months), PRP injection was associated with a larger improvement in VAS scores than corticosteroid injection (4 randomized controlled trials [RCTs]; N=314; mean difference [MD] –2.9; 95% CI, –4.9 to –0.79). In short-term follow-up (<2 months), VAS score improvements were similar between PRP and corticosteroid injections (6 RCTs; N=445; MD 0.85; 95% CI, –0.35 to 2.0). Limitations included variations in preparation, volume, and concentration of PRP injections; and lack of subject or researcher blinding to the injectate because of differences in appearance.

A 2019 RCT (n=80) compared PRP and corticosteroid injections for the treatment of lateral epicondylitis pain.[2] The trial included patients 18 years old or older diagnosed with lateral epicondylitis who had failed at least three months of conservative therapy (not defined). Patients were excluded if the differential diagnosis for elbow pain included cervical radiculopathy, osteochondritis dissecans, rheumatoid disorders, or diabetes. Participants were evenly and randomly allocated to receive either a single treatment of PRP injection or corticosteroid injection. The treatment of 3 mL of PRP was prepared using a double-spin method (160 g for 12 minutes and then 460 g for 18 minutes at room temperature). The corticosteroid group received 40 mg of triamcinolone with 2% xylocaine. The treatments were injected by palpation (without ultrasound guidance) into the undersurface of the extensor carpi radialis brevis and the common extensor tendon using a single skin penetration with 10 to 20 tendon penetrations. The primary outcome was pain (using VAS, 0 to 100 scale) measured at six weeks, three months, and one year after intervention. At baseline, the corticosteroid group had a mean VAS score of 81, and the PRP group had a mean VAS score of 77. At six weeks, corticosteroid injection was associated with a larger improvement in VAS score compared with PRP injection (mean VAS score 14 vs 45; $P<.001$). PRP injection was associated with larger improvements in VAS score at three months (mean VAS score 4.0 vs 23; $P=.002$) as well as one year (mean VAS score 2.5 vs 14; $P=.02$) compared with corticosteroid injection. CIs were not reported. Limitations included absence of blinding to injectate as well as subject recruitment from a single center. Additionally, the reduction in pain for both groups at 12 months may partially reflect the

natural course of the condition and not solely the effect of the treatments. EBP

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In patients with dementia, which pharmaceutical intervention is best at reducing agitated behaviors?

EVIDENCE-BASED ANSWER

In patients with dementia, atypical antipsychotics (such as risperidone) double the odds of a 50% improvement over placebo, although the usual magnitude of improvement is small (SOR: **A**, meta-analyses). Dextromethorphan/quinidine also seems to relieve symptoms of agitation (SOR: **A**, meta-analysis).

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A 2017 meta-analysis of 36 randomized controlled trials (RCTs; N=5,585) assessed the use of pharmacological treatments for agitation in patients with all forms of dementia.[1] The participants were mostly female with a mean age of 82 years old and a baseline mini-mental status score of 10 (indicating moderate dementia). Antipsychotics examined included risperidone (11 of 36 studies), followed by haloperidol (7 of 36 studies) and quetiapine (4 of 36 studies). Additional studies included treatment with valproate (5 of 36 studies) or dextromethorphan/quinidine (1 of 36 studies). All pharmacological treatments were compared with placebo. Dosing, treatment regimens, and the number of patients in pooled outcomes were not reported. Many validated scales used throughout the studies and results were pooled and reported as odds ratios (ORs) of agitation improving by 50% from baseline over an eight-week period. After eight weeks, a significant improvement was noted in symptoms for risperidone (11 studies, OR 1.9; 95% CI, 1.5–2.4) and dextromethorphan/quinidine (1 study, OR 3.0; 95% CI, 1.7–5.5) when compared with placebo.

A 2015 meta-analysis of 32 RCTs (N=6,812) evaluated the efficacy of pharmacological management for neuropsychiatric symptoms in patients with dementia.[2] Patients were all diagnosed with probable or possible Alzheimer dementia following criteria from the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition* or the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association. Severity of dementia ranged from mild to severe, with baseline Mini-Mental State Examination scores of 4.5 to 21. The mean ages of the participants were around 79 years old. Treatment consisted of cholinesterase inhibitors (15 trials, N=5,038), atypical antipsychotics (6 trials, N=2,511), antidepressants (2 trials, N=288), mood stabilizers (1 trial, n=27), and memantine (8 trials, N=2,829) all compared versus placebo. Oral formulations of medication were used, except for one study that used intramuscular aripiprazole and one study of transdermal estrogen. The median trial duration was 56 days (range 1–90 days). Outcomes assessed were improvement in behavioral and psychological symptoms of dementia and were measured by the Neuropsychiatric Inventory scale. For simplicity, results were pooled and converted into a standardized mean difference (SMD). A small improvement was noted in behavioral and psychological symptoms with atypical antipsychotics (SMD –0.21; 95% CI, –0.29 to –0.12) and a slight improvement of questionable clinical significance with cholinesterase inhibitors (SMD –0.12; 95% CI, –0.23 to –0.02) when compared

with placebo. No other included medications resulted in improvements. EBP

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What is the risk of hypoglycemia in infants born to mothers on beta-blocker therapy?

EVIDENCE-BASED ANSWER

Risk of hypoglycemia in infants born to mothers on beta-blocker therapy remains unclear. Beta-blocker therapy in pregnancy may increase the risk of neonatal hypoglycemia, although any association is seen primarily in low-quality evidence (SOR: **C**, conflicting randomized controlled trials and cohort studies).

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A 2018 systematic review of eight randomized controlled trials (RCTs; N=5,909) evaluated the effect of treatment of hypertension in pregnancy on the development of severe hypertension, proteinuria, and pre-eclampsia.[1] A subanalysis of two double-blinded RCTs (N=272) specifically evaluated the incidence of hypoglycemia for infants born to mothers on beta-blocker therapy. All patients were pregnant women with single or multiple gestation with mild or moderate hypertension (systolic blood pressure of 140–169 mmHg, diastolic blood pressure of 90–109 mmHg). Patients were between 20 and 38 weeks at study entry in one trial and in the third trimester in the second trial. Women were randomized to 50–200 mg daily of atenolol, 100–200 mg twice daily of labetalol, or placebo for at least seven days. Neonatal hypoglycemia was not specifically defined and results were adjusted for gestational age. Mothers treated with beta-blockers versus placebo did not have higher rates of neonatal hypoglycemia (adjusted risk ratio [aRR] 0.71; 95% CI, 0.13–3.83).

A 2017 systematic review of 47 cohort studies and RCTs examined the effects of antihypertensive medications administered in utero on neonatal and child health outcomes.[2] A subanalysis of two cohort studies (N=87,536) and four RCTs (N=759) specifically examining exposure to beta-blockers and the risk of neonatal hypoglycemia were identified. The RCTs were included in the above systematic review and thus will not be summarized. The first cohort study conducted in the United States (n=87,407) evaluated pregnant women exposed to various beta-blockers in the third trimester compared with no use of hypertensive medications. Treatment durations, dosing regimens, and drug types were not specified. Beta-blocker exposure was associated with higher rates of neonatal hypoglycemia compared with those born to mothers not on treatment (RR 3.1; 95% CI, 2.2–4.2). The second cohort study conducted in India (n=129) evaluated exposure to labetalol (dosing not given) compared with other hypertensives during pregnancy. Labetalol therapy was associated with an increased incidence of hypoglycemia compared with various other hypertensives (48% vs 17%, P=.01).

A 2016 retrospective cohort study of over two million pregnancies in the United States analyzed the risk of neonatal hypoglycemia and bradycardia after in utero exposure to beta-blockers (n=10,585).[3] Pregnant women enrolled in Medicaid who were prescribed beta-blockers (including alpha- and beta-blockers and combination drugs) at the time of delivery were included. The authors defined neonatal hypoglycemia as documentation of hypoglycemia in the newborn by a clinician in the medical record, a glucose level of 45 mg/dL or less, or

treatment with intravenous glucose or a prescribed increased frequency of feeding. The primary outcomes were rates of hypoglycemia and bradycardia in beta-blocker–exposed pregnancies compared with nonexposed. Propensity scores were used to match exposed subjects with similar nonexposed subjects to control for potential confounding variables. Beta-blocker exposure during pregnancy was associated with neonatal hypoglycemia when compared with nonexposure (adjusted odds ratio 1.68; 95% CI, 1.50–18.9). EBP

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Is sleep duration associated with symptom improvement in athletes with sports-related concussion?

EVIDENCE-BASED ANSWER

In athletes with sports-related concussion, sleeping less correlates with increased symptoms and symptom severity (SOR: **B**, a prospective cohort study). However, changes in baseline sleep do not affect days to recovery from concussion (SOR: **B**, a prospective cohort study).

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A 2018 prospective cohort study (n=971) aimed to determine if sleep quantity and disturbance are associated with concussion symptoms after a sports-related concussion.[1] The cohort included young athletes (8–18 years old) participating in various sports, diagnosed with sports-related concussion. Patients were matched with control athletes who had never been diagnosed with a concussion. Sleep duration the night before the assessment was self-reported by participants. Symptoms of concussion, including number of sleep disturbances, migraine symptoms, and neuropsychological symptoms (eg, irritability and nervousness), were assessed using the Post-Concussion Symptom Scale and Immediate Post-Concussion Assessment and Cognitive Testing assessments. Symptoms were assessed within seven days of concussion and at 21 days or more post-concussion. Results from statistical analyses were described using Pearson correlation coefficient (*r*), where values greater than 0.4 represent strong correlation, 0.2 to 0.4 moderate correlation, and less than 0.2 are considered weakly correlated. During the acute post-concussion phase, less sleep quantity in the concussion group was not correlated with post-concussion symptoms other than a greater report of sleep disturbances ($r=-0.14$, $P=.002$). At 21 days or more post-concussion, less sleep quantity in the sports-related concussion group was weakly correlated with greater self-report of migraine symptoms ($r=-0.15$, $P=.001$) and neuropsychological symptoms ($r=-0.10$, $P=.024$). Limitations included potential for reporting bias with self-reported sleep measures and those typical to cohort studies including risk of confounders and the inability to determine causation.

A 2017 prospective cohort study (n=130) assessed whether decreased sleep duration after concussion was associated with time to recovery and performance.[2] Patients included collegiate athletes (mean age of 19 years old) diagnosed with concussion. Those with a history of three or more concussions, sleep disorder, learning disability, ADHD, or substance abuse were excluded. Patients were categorized according to their sleep change as follows: getting less sleep than baseline by at least one hour, getting approximately the same amount of sleep within one hour of baseline, or getting more sleep than baseline by at least one hour. Symptom severity scoring was conducted using the Sports Concussion Assessment Tool Three (scores range 0–132, assessing 22 symptoms, higher score indicating worse symptoms). Baseline assessment was done at any point before concussion ranging from several months to a few days. Patients were then assessed within 24 to 48 hours of injury, daily after diagnosis, "day of asymptomatic," and after return-to-play. "Day of asymptomatic" was defined as the day medical clearance was provided to begin a gradual return-to-play protocol. Sleep groups did not differ in days to asymptomatic (shorter sleep mean 7.3, no sleep change 7.2, longer sleep 6.2 days after concussion, $P=.18$). At 24 to 48 hours, the shorter sleep group had greater symptom severity than no sleep change (39 vs 25, $P=.007$) and longer sleep (39 vs 25, $P=.004$). The shorter sleep group had higher average symptom severity at all time points compared with the no sleep change (14 vs 8.3, $P=.022$) and longer sleep groups (14 vs 8.9, $P=.012$). Limitations included potential for reporting bias with self-reported sleep duration.

A 2015 cross-sectional study (n=545) evaluated for a correlation between sleep duration and symptom severity after a concussion.[3] The study included adolescent athletes (11–18 years old) treated for sports-related concussion. Patients were stratified based on both sleep duration and sleep disturbance symptoms. Sleep duration was categorized into patients sleeping less than seven hours, between 7 and 9 hours, and greater than nine hours. Sleep disturbance was categorized into patients having trouble falling asleep, sleeping less than normal, sleeping more than normal, or no sleep disturbance. Patients completed the Post-Concussion Symptom Scale (self-reported symptoms, scores ranging 0–132, higher scores indicate worse symptoms) at three specific time points determined by the treating provider throughout the recovery phase. Sleeping less than seven hours the night before testing correlated with higher self-reported symptom scores on initial testing compared with 7 to 9 hours and greater than nine hours of sleep (27 vs 8.7 vs 23, $P<.001$). Sleeping more than normal and sleeping less than normal correlated with higher self-reported symptom scores compared with no sleep change at all time points (27 vs 23 vs 8.7, 17 vs 17 vs 3.2, 21 vs 32 vs 3.5, $P<.001$). Limitations included potential for reporting bias with self-reported sleep quantity and changes. EBP

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Are 5-HT1 receptor agonists ("triptans") more effective than ibuprofen in the treatment of migraine in children and adolescents?

EVIDENCE-BASED ANSWER

No studies directly compare ibuprofen with 5-HT1 receptor agonists in pediatric patients. Ibuprofen and 5-HT1 receptor agonists as a class are both moderately more effective than placebo at producing pain freedom at two hours posttreatment in children and adolescents (SOR: **A**, meta-analysis of randomized controlled trials). The American Academy of Neurology and American Headache Society recommends sumatriptan alone, sumatriptan combined with naproxen, zolmitriptan, or ibuprofen alone as more likely than placebo to relieve migraine headache in children and adolescents (SOR: **C**, consensus guideline).

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A 2016 meta-analysis of 26 prospective, placebo-controlled, randomized trials (N=9,158 enrolled; 7,630 received medication) compared the efficacy of ibuprofen and various 5-HT1 receptor agonists to placebo in reducing pain in children.[1] The study compared the efficacy of ibuprofen, almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan versus placebo for the outcome of pain freedom two hours after treatment of pediatric migraine. The meta-analysis included studies involving pediatric participants 17 years old or younger with a diagnosis of migraine with or without aura. Medications were given at standard doses (see **TABLE 1**). Pain freedom was defined as the absence of pain at two hours posttreatment and before use of any additional or rescue medication. Ibuprofen was more effective than placebo at two hours posttreatment for producing pain freedom in children <12 years old. Though sumatriptan and rizatriptan individually did not outperform placebo in children <12 years old, pooled data demonstrated that 5-HT1 receptor agonists, as a class, were more effective than placebo at producing pain freedom at two hours posttreatment in this age group. In adolescents 12 to 17 years old, 5-HT1 receptor agonists were also more effective than placebo. In this age range, the only 5-HT1 receptor agonists to demonstrate effectiveness individually compared with placebo were sumatriptan, rizatriptan, and zolmitriptan.

A 2019 practice guideline from the American Academy of Neurology and the American Headache Society evaluated the question of whether acute self-administration of treatments, compared with placebo, reduced headache pain in children and adolescents with migraine.[2] The authors systematically reviewed all randomized controlled trials published between 2003 and 2017 that evaluated acute migraine treatments in children and adolescents. The authors included outcomes that evaluated headache pain relief at specific time points after intervention. The systematic review

TABLE 1. Headache relief and pain freedom at two hours posttreatment with ibuprofen and various 5-HT1 receptor agonists in children and adolescents compared with placebo[1]

Study drug	Dosage	Age of patients (in years)	No. of studies	No. of patients	Relative risk of being pain-free 2 hours posttreatment (95% CI)
Ibuprofen	7.5 or 10 mg/kg	<12	2	125	1.87 (1.15–3.04)
All 5-HT1 receptor agonists	n/a	<12	3	345	1.67 (1.06–2.62)

TABLE 1. Headache relief and pain freedom at two hours posttreatment with ibuprofen and various 5-HT1 receptor agonists in children and adolescents compared with placebo[1] *(Continued)*

Study drug	Dosage	Age of patients (in years)	No. of studies	No. of patients	Relative risk of being pain-free 2 hours posttreatment (95% CI)
All 5-HT1 receptor agonists	n/a	12–17	21	6,761	1.32 (1.19–1.47)
Sumatriptan	5–20 mg intranasal or 50–100 mg oral (20 mg intranasal most common)	<12	2	145	2.29 (1.00–5.23)
Sumatriptan	5–20 mg intranasal or 50–100 mg oral (20 mg intranasal most common)	12–17	10	2,415	1.27 (1.10–1.48)
Rizatriptan	5–10 mg oral	<12	1	200	1.31 (0.89–1.92)
Rizatriptan	5–10 mg oral	12–17	2	1,526	1.34 (1.13–1.60)
Zolmitriptan	2.5, 5, or 10 mg oral or 5 mg intranasal	12–17	4	1,532	1.66 (1.16–2.38)
Almotriptan	6.25, 12.5, or 25 mg oral	12–17	1	714	1.10 (0.88–1.39)
Eletriptan	40 mg oral	12–17	1	274	1.46 (0.88–2.43)
Naratriptan	0.25, 1.0, or 2.5 mg oral	12–17	1	300	1.06 (0.65–1.75)

found that children and adolescents receiving sumatriptan alone, sumatriptan combined with naproxen, zolmitriptan, or ibuprofen alone were more likely than those receiving placebo to be free of headache pain at two hours (see **TABLE 2**). Limitations involved the breadth of variations in endpoints used in trials. Examples of these variations included headache relief at one- and two-hour posttreatment, relief of headache-associated symptoms,

TABLE 2. Headache pain-free at one and two hours posttreatment with ibuprofen and various 5-HT1 receptor agonists in children and adolescents[2]

Outcome	High confidence (more likely than placebo)	Moderate confidence (probably more likely than placebo)	Low confidence (possibly more likely than placebo)	Low confidence (possibly no more likely than placebo)
Pain-free at 1 hour		Zolmitriptan nasal spray (NS) 5 mg		
Pain-free at 2 hours	Sumatriptan/naproxen oral tablet (OT) 10/60 mg Sumatriptan/naproxen OT 30/180 mg Sumatriptan/naproxen OT 85/500 mg Zolmitriptan NS 5 mg	Ibuprofen oral solution 7.5-10 mg/kg Sumatriptan NS 20 mg	Rizatriptan oral dissolving tablet 5 or 10 mg	Almotriptan OT 12.5 mg

pain-free at one hour posttreatment, and pain-free at two hours posttreatment. EBP

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