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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

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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.

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DISCLOSURE

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Do serial measurements of natriuretic peptides (BNP or NT-proBNP) help guide therapy in patients with chronic heart failure and improve outcomes?

EVIDENCE-BASED ANSWER

Yes. Therapy guided by serial measurement of cardiac natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-B-type natriuretic peptide [NT-proBNP]) reduces all-cause mortality and heart failure–related admission compared with symptom guided therapy (SOR: **A**, meta-analysis of randomized controlled trials [RCTs] and single RCT). Guiding treatment by BNP or NT-proBNP may be less effective in patients over 75 years old (SOR: **B**, subanalysis in meta-analysis of RCTs).

DOI 10.1097/EBP.0000000000001143

A 2013 meta-analysis of 12 RCTs (N=2,686) evaluated whether natriuretic peptide–guided therapy improved mortality and hospitalization rates compared with clinically guided therapy in patients with chronic heart failure.[1] Patients had a mean age of 70 years old (range 61–78 years old), an average of New York Heart Association (NYHA) class of between I and II, and average left ventricular ejection fraction of 29% (range 20–39%). All studies randomized patients to a treatment group where either BNP or NT-proBNP were used to guide titration of standard recommended pharmacological treatments such as ACE inhibitors, angiotensin receptor blockers, beta-blockers, etc. to treat chronic heart failure (N=1,245), or a standard titration of therapy based on clinical symptoms (N=1,441). Patients were followed for a mean of 14 months (range 4 months to 3 years) and all randomized trials reported all-cause mortality, heart failure–related hospitalization, and all-cause hospitalization as clinical endpoints. When compared with the standard clinical therapy group, the BNP-guided group had significantly lower all-cause mortality (odds ratio [OR] 0.74; 95% CI, 0.60–0.91) and hospitalization from heart failure (OR 0.55; 95% CI, 0.40–0.77), but not all-cause hospitalization (OR 0.80; 95% CI, 0.63–1.02). Secondary analysis and comparisons of patients less than or equal to 75 years old (n=556) and those older than 75 years old (n=587) were compared from three trials. The composite for all-cause mortality and heart failure–related admission was significantly lower in the BNP and NT-proBNP cohorts in patients 75 years old or younger compared with those over 75 years old (OR 0.45; 95% CI, 0.21–0.97).

A 2009 RCT (N=499), the largest trial included in the above meta-analysis, examined whether N-terminal BNP–guided heart failure therapy showed benefit in treating patients with heart failure.[2] Patients included were 60 years old or older with systolic heart failure (ejection fraction ≤45%), possessed a NYHA class of II or greater, prior hospitalization for heart failure within one year, and N-terminal BNP level of two or more times the upper limit of normal. These patients were randomized to receive uptitration of guideline-based treatment based on BNP levels or based on NYHA symptom classification. The study had an 18-month follow-up and measured all-cause hospitalizations, heart failure–related hospitalizations, and quality of life as assessed by structured validated questionnaires. Although similar rates of survival free of all-cause hospitalizations (41% vs 40%, $P>.05$) and similar improvements in quality of life metrics were noted, a significantly higher rate of survival without CHF hospitalization was seen in the N-terminal BNP-guided group (72% vs 62%, $P<.05$) compared with the symptom-guided treatment group. No significant difference in quality of life was observed between the two groups. EBP

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The authors declare no conflicts of interest.

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Barrett's esophagus: is more better?

Jankowski JAZ, de Caestecker J, Love SB, et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. *Lancet*. 2018; 392(10145): 400–408. Erratum in: *Lancet*. 2018 Dec 15; 392(10164): 2552.

DOI 10.1097/EBP.0000000000000640

This is a randomized factorial trial comparing the use of high-dose proton pump inhibitor (PPI) esomeprazole and aspirin to standard care in Barrett's esophagus. Some 2,557 patients (predominately White) who met the globally accepted criteria for Barrett's esophagus were recruited from 84 medical centers. The patients were randomized to four groups of low-dose PPI (20 mg daily), low-dose PPI and aspirin (300–325 mg daily), high-dose PPI (40 mg twice daily), and high-dose PPI and aspirin. Patients were followed for at least eight years. Clinicians knew the medications being used, but pathologists were masked to treatment groups. The primary composite endpoint was time to all-cause mortality, esophageal adenocarcinoma, or high-grade dysplasia, which was analyzed with accelerated failure time modeling adjusted for minimization factors.

Using intention-to-treat analysis, accelerated failure time modelling was interpreted in the time to an event using the time ratio (TR). The PPI+aspirin group endpoints did not reach significance (P=.28, n=2,280, TR 1.3; 95%, CI, 0.81–2.09), so PPI and aspirin were compared separately. High-dose PPI was found to be significantly more effective than low-dose PPI (TR 1.27; 95% CI, 1.01–1.58, P=.038). If the expected time to composite event while taking low-dose PPI was eight years, taking high-dose PPI increased this to 10.2 years (95% CI, 8.1–12.6).

In the primary analysis of aspirin, the effect of aspirin was not significantly different from no aspirin. One of the exclusion criteria was NSAID use, but the UK sites collected information on NSAID initiation and use. In the subgroup not taking NSAIDs, aspirin therapy reached significance compared with no aspirin for the composite endpoint (TR=1.29; 95% CI, 1.01–1.66, P=.043). High-dose PPI with aspirin may have had an additive benefit (TR=1.38; 95% CI, 0.98–1.94, P=.068), but it was not statistically significant as the trial was not powered for this analysis.

In patients with Barrett's esophagus, the estimated number needed to treat with high-dose PPI versus low-dose PPI to prevent high-grade dysplasia, adenocarcinoma, or death was 34, and the estimated NNT with aspirin was 43 in patients not using NSAIDs. Although few of the individual endpoints reached statistical significance, reduced all-cause mortality was noted with high-dose versus low-dose PPI (TR=1.36; 95% CI, 1.01–1.82, P=.039).

A key weakness was that 44% of subjects dropped out. And, the study did not take into account the risks related to long-term PPI or aspirin use that have recently been published.

Methods

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

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

Bottom line: A small benefit is observed in composite outcomes with high-dose PPI therapy in patients with Barrett's esophagus. This study did not specifically consider the long-term risks of high-dose PPI treatment and had a very high dropout rate. Further study to elaborate on these deficiencies is needed. Clinicians may consider using high-dose PPIs (and aspirin) in Barrett's esophagus after discussing the risks and benefits of the therapy with the patient.

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First-line antihypertensives, still dealer's choice

Suchard MA, Schuemie MJ, Krumholz HM, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. *Lancet*. 201916; 394(10211): 1816–1826.

DOI 10.1097/EBP.0000000000001094

This systematic, multinational large scale analysis used real-world data to evaluate the comparative effectiveness of initial hypertension monotherapy in treatment naïve patients. The data for 4.9 million public and private patients aged 18 to 65 years old from the United States, Japan, South Korea, and Germany were compiled from six administrative claims databases and three Electronic Medical Records.

Propensity score stratification was used to balance baseline patient characteristics including sex, age, and general or cardiovascular-specific medical history. Patients were variable-ratio matched by propensity score, and the Cox proportional hazards model was used to estimate hazard ratios (HRs), which were then aggregated. There were three primary (acute myocardial infarction, hospitalization for heart failure, and stroke), six secondary, and 46 safety outcomes evaluated among patients started on thiazide or thiazide-like diuretics (THZ), angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers, dihydropyridine calcium channel blockers, or nondihydropyridine calcium channel blockers (ndCCBs). Of the 22,000 calibrated HRs generated, most showed no effectiveness differences between classes. The only head to head comparison with a statistically significant difference favored THZ over ACEi for reducing risk of acute myocardial infarct (HR 0.84, 95% CI 0.75–0.95), hospitalization for heart failure (HR 0.83, 95%CI 0.74–0.95), and stroke (HR 0.83, 95% CI 0.74–0.95). Safety profiles in this comparison also favored THZs over ACEi. The ndCCB class was significantly inferior to the other four classes for all primary and secondary outcomes. Limitations of the study were mainly because of the heterogeneity in the disparate secondary data sets, which limited available data for subgroup analysis. Specifically, blood pressure measurement data were not available in all data sources. Although post hoc analysis did not reveal a meaningfully different effect size, it is unclear if baseline data for all patients would affect study outcomes.

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	No	Clinically meaningful	No

Bottom line: Overall, this study's outcomes reinforce current guideline recommendations that no significant effectiveness difference exists between the most common antihypertensive classes (ACEi, thiazide diuretics, and CCBs). The only statistically significant difference favored thiazide diuretics over ACEi; however, this superiority did not extend to thiazides and CCBs, nor CCBs and ACEi. For most patients being initiated on antihypertensive monotherapy, these results did not demonstrate a superiority between CCBs and thiazides that would change prescribing practices.

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17-OHPC does not significantly reduce recurrent preterm birth in women with prior spontaneous preterm birth

Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG study): a multicenter, international, randomized double-blind trial. *Am J Perinatol*. 2020; 37(2): 127–136.

DOI 10.1097/EBP.0000000000001128

This double-blind, placebo-controlled, international trial at 93 centers across nine countries randomized 1,708 pregnant patients with singleton gestations and history of spontaneous preterm birth (PTB) to receive

either weekly injections of 250-mg 17-α-hydroxyprogesterone caproate (17-OHPC) or placebo to assess if the medication could reduce the risk of recurrent PTB. This study was completed after 17-OHPC had become an acceptable standard of care in the United States for women with pregnancy complicated by prior PTB based on a 2003 trial that stopped early because of the notable significant benefit of treatment. For this study, women aged 18 years or older with a singleton pregnancy between 16 0/7 weeks and 20 6/7 weeks of gestational age who had history of singleton spontaneous PTB (defined as delivery from 20 0/7 to 36 6/7 weeks following spontaneous preterm labor or preterm premature rupture of membranes) were eligible for the trial. The primary outcomes were PTB less than 35 weeks (including all deliveries occurring from randomization until 35 0/7 weeks) and a composite neonatal morbidity and mortality index, which included neonatal death, grade-three or four intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, or proven sepsis. No difference between treatment groups was found for either of these primary outcomes: PTB occurred in 11.0% of the 17-OHPC group verses 11.5% in the placebo group (risk ratio [RR], 0.95 with 95% CI, 0.71–1.26 and $P=.72$), and neonatal composite index was 5.6% in the 17-OHPC group verses 5.0% for the placebo (RR, 1.12 with 95% CI, 0.70–1.66 and $P=.73$). Secondary outcomes were neonatal death, PTB less than 32 0/7 weeks, PTB less than 37 0/7 weeks, as well as spontaneous and medically indicated PTB less than 32 0/7, 35 0/7, and 37 0/7 weeks. No differences were noted noted in any of these areas between the treatment and placebo groups.

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	No	Clinically meaningful	Yes

Bottom line: Use of 17-OHPC does not reduce the risk of PTB in women with prior spontaneous PTB compared with placebo, despite previous trials that noted very significant reduction in recurrent PTB risk.

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Dapagliflozin, not just for diabetes anymore

Dapagliflozin in patients with heart failure and reduced ejection fraction

McMurray JJV, DeMets DL, Inzucchi SE, et al. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). Eur J Heart Fail. 2019;21(5): 665-675. DOI 10.1002/ejhf.1432

KEY TAKEAWAY: Use of dapagliflozin 10 mg daily in patients with heart failure with reduced ejection fraction (HFrEF) with and without diabetes reduces the risk of worsening heart failure or death from cardiovascular disease.

BACKGROUND: The addition of sodium-glucose cotransporter inhibitors in patients with type 2 diabetes and HFrEF reduces the rate of hospitalizations because of exacerbation of heart failure or death from cardiovascular causes. No randomized controlled trial (RCT) had yet explored whether these benefits could be seen in a nondiabetic population.
PATIENTS: Patients with stage II to IV HFrEF; 55% of the participants did not have type 2 diabetes at baseline.
INTERVENTION: Dapagliflozin 10 mg daily
CONTROL: Placebo + current recommended medical therapy
OUTCOME: Composite of worsening of heart failure or cardiovascular death

LEVEL OF EVIDENCE: STEP 2

STUDY DESIGN: RCT

METHODS BRIEF DESCRIPTION: The RCT evaluated the combined rate of HFrEF exacerbations or cardiovascular mortality after the addition of dapagliflozin to medical therapy for HFrEF in patients with and without type 2 diabetes. Participants were randomized to dapagliflozin 10 mg daily or placebo. Patients additionally received guideline-directed heart failure therapy per provider discretion. Patients were evaluated at 14 days, 60 days, and four months postrandomization, and then every four months.

INTERVENTION (# IN THE GROUP): 2,368

COMPARISON (# IN THE GROUP): 2,368

FOLLOW-UP PERIOD: Planned follow-up of 24 months (median 18.2 months)

RESULTS:
- The primary outcome of worsening heart failure or death from cardiovascular causes occurred less in the dapagliflozin group versus the placebo (16% vs 21%; hazard ratio [HR] 0.74; 95% CI, 0.65–0.85; number needed to treat [NNT]=21). Worsening of heart failure events occurred less in the dapagliflozin group (10% vs 14%; HR=0.70; 95% CI, 0.59–0.83). Death from cardiovascular causes occurred less in the dapagliflozin group (9.6% vs 12%; HR=0.82; 95% CI, 0.69–0.98; NNT=47).
- No significant safety concerns with dapagliflozin were observed, and adverse events were low and similar between the groups (7.5% vs 6.8%).
- The benefit to the primary outcome was seen in both the diabetic and non-diabetic subgroups.

LIMITATIONS: Less than 5% of patients were Black and few very elderly patients enrolled. The low number of study patients taking sacubitril-valsartan, which has been shown to be superior to angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in this population. This study was funded by the manufacturer of dapaglifozin. EBP

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OMT for migraine and mood disorders

Effects of osteopathic manipulative therapy on pain and mood disorders in patients with high-frequency migraine

Dippolito M, Tramontano M, Buzzi MG. Effects of osteopathic manipulative therapy on pain and mood disorders in patients with high-frequency migraine. *J Am Osteop Assoc*. 2017;117(6):365. DOI 10.1097/EBP.0000000000001044

KEY TAKEAWAY: In this retrospective cohort, patients with high-frequency migraine and comorbid mood disorders showed small but not clinically meaningful improvement over baseline on some headache and mood disorder questionnaires after four 45-minute osteopathic manipulative therapy (OMT) sessions.

STUDY DESIGN: Retrospective cohort.

LEVEL OF EVIDENCE: STEP 4.

BRIEF BACKGROUND INFO: OMT is a nonpharmacological treatment used by osteopathic physicians to treat musculoskeletal and other medical complaints. This retrospective study evaluated the effect of OMT in patients with high-frequency migraines and comorbid mood disorders.

PATIENTS: Patients with high-frequency migraine treated with OMT at a headache clinic in Italy from 2011 to 2015; mean age was 47.5 years, and 55% were female

INTERVENTION: OMT (4 × 45 minute sessions)

CONTROL: N/A (no control group)

OUTCOME: Pre/post comparison on the Headache Disability Inventory (HDI), the Headache Impact Test (HIT-6), the Hamilton Depression Rating Scale (HDRS), the State-Trait Anxiety Inventory (STAI) forms X-1 and X-2, and the number of migraines per month.

METHODS BRIEF DESCRIPTION:
- Inclusion criteria: high-frequency migraines >8 and <15 days per month, received OMT, psychological evaluation before/after OMT.
- Exclusion criteria: nonmigraine headache diagnosis or somatic or psychiatric disorders (major depression, psychosis), comorbid musculoskeletal, neurologic, and rheumatic diseases.
- OMT sessions (4 × 45 minutes) were provided by the same osteopath, but techniques used were individualized.
- All patients completed the same questionnaires at baseline and at eight weeks: HDI, HIT-6, HDRS, STAI X-1 and X2, and migraine frequency.

INTERVENTION (# in the group): 11

COMPARISON (# in the group): 0

FOLLOW-UP PERIOD: 8 weeks

RESULTS: Upon reevaluation at eight weeks after completing the four OMT sessions, there were significant improvements in patient scores compared with baseline on the HDI (58.2 vs 45.1; $P<.05$), HIT-6 (63 vs 56.2; $P<.05$), and the STAI X-2 (43.2 vs 39.4; $P<.05$). However, none met the minimum clinically significant improvement required for each questionnaire.

There were no significant changes noted in pre/post scores on the STAI X-1, HDRS, or frequency of migraines (all $P>.05$).

LIMITATIONS:
- Study design cannot prove causal associations.
- Small sample size.
- OMT protocol not standardized
- Nearly all statistically significant findings not clinically significant. EBP

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The authors declare no conflicts of interest.

Do exercise interventions improve frailty in older adults?

Case

You are seeing an 81-year-old woman who reports that she has been feeling generally weak for the past year, limiting her physical activity. She has not fallen but states she is afraid of falling. She lives in a single-story condominium and denies any significant medical or psychosocial changes over the past year. Her supportive daughter attends the clinic visit and asks if exercise would help her mom.

DOI 10.1097/EBP.0000000000001179

EVIDENCE-BASED ANSWER

Multicomponent exercise interventions may reverse frailty in frail, community-dwelling, older adults based on evidence from small, heterogeneous randomized control trials (RCTs).

EVIDENCE SUMMARY

A systematic review of nine RCTs examined the effect of exercise interventions on markers of frailty in older adults.[1] Of the nine included RCTs, six included multicomponent exercise interventions consisting of strength, balance, and walking exercises; the remaining three intervention programs were based on strength training. The systematic review determined that exercise interventions improve the overall function of older adults who are frail and can have positive effects on frailty criteria. Of five articles studying the effects of exercise on falls, three found that exercise interventions decreased falls incidence or the fear of falling. Four of six RCTs reporting on mobility suggested improvements in outcome measures (eg, Timed Up and Go and chair rise), whereas one of three RCTs that measured balance demonstrated improved scores on the Berg Balance Scale. Two of four studies measuring functional ability reported improved function (eg, the Barthel Index). Significant muscle strength gains occurred in five of seven RCTs. Only one study applied the Fried frailty criteria[2] and demonstrated that the exercise intervention reversed frailty status. Overall, the systematic review was methodologically limited by exercise intervention variability, inconsistent outcome measures, and small sample sizes. This systematic review concluded that exercise improves overall function of older adults who are frail; however, the interventions and outcome measures were heterogeneous.

A RCT (N=131) included in the above systematic review studied the combined and separate effects of exercise and milk fat globule membrane (MFGM) supplementation on frailty in frail, community-dwelling, Japanese women more than 75 years old.[3] The exercise group attended a moderate-intensity training program twice a week for three months. Each 60-minute session included a warm-up and cool-down period with 30 minutes of strengthening exercises and 20 minutes of balance and gait training exercises. Compared with controls, the exercise group demonstrated reversal of several of the Fried frailty criteria,[2] including weight loss, exhaustion, low physical activity, and slow walking speed. However, muscle strength did not significantly change. At the four-month follow-up, exercise appeared critical to frailty reversal because, compared with placebo, significant differences were observed in the exercise+MFGM group (adjusted odds ratio [aOR] 4.7; 95% CI, 1.5–15) and exercise+placebo group (aOR 3.6; 95% CI, 1.1–12), but not the MFGM only group (aOR 1.9; 95% CI, 0.5–6.5).[3] The gender, height, and body mass index of the study population differ from the population used to develop the Fried definitions of frailty; therefore, generalizability of these findings may be limited. This RCT suggests that a supervised exercise program consisting of strength, gait, and balance exercises can reverse frailty.

A RCT (N=319) studied the effect of three months of individualized home-based exercise, nutrition, and combination interventions on frailty in prefrail or frail older adults.[4] Physiotherapists provided individualized exercises, including strength, endurance, flexibility, and balance exercises. Participants performed 3 to 5 exercise sessions per week ranging from 5 to 60 minutes per session. At the six-month follow-up, there were significant improvements in frailty scores in all three intervention groups compared with placebo, exercise group (difference in frailty score baseline to 6 month change –0.23 [95% CI, –0.41 to –0.05], $P=.012$), nutrition group (–0.28 [95% CI, –0.46 to –0.11], $P=.002$) and combined nutrition and exercise group (–0.34, [95% CI, –0.52 to –0.16], $P<.001$).[4] Although an intention to treat analysis was performed, attrition (22% at 6 months) may have biased the study results, and exercise adherence was not reported. However, the authors concluded

that exercise, alone or in combination with improved nutrition, can reverse frailty.

Case Conclusion

You respond to the patient and her daughter that a multimodal exercise program may reverse frailty. Properly prescribed exercise has the potential to improve the perceived weakness, declining physical activity, and uncertain balance that are contributing to the patient's frailty. EBP

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Does ondansetron reduce the need for hospitalization or IV fluids in children with AGE?

CASE STUDY

You are seeing a four-year-old girl in clinic for one day of presumed viral vomiting and diarrhea. She looks well, is tolerating liquids, and starting to take some solids. Her mother asks about medication you can give her to stop the vomiting next time this happens, as she recalls her son was once given ondansetron for a similar illness.

DOI 10.1097/EBP.0000000000001205

Bottom Line

Oral ondansetron likely does not reduce the need for IV rehydration in children with diarrhea and vomiting without dehydration, as defined by the WHO dehydration tool (see **TABLE**).

Evidence Summary

There are about two million emergency department visits annually in the United States for pediatric gastroenteritis.[1] Although there is strong evidence showing that ondansetron can be helpful in preventing the need for intravenous fluids and hospital admission for dehydrated children,[2,3] there has been less research specifically about its use in nondehydrated children presenting to ambulatory settings with diarrhea and vomiting. A randomized, double-blind, placebo-controlled trial compared oral ondansetron with placebo in 626 children of 0.5 to 5 years old who presented to the emergency department in Karachi, Pakistan, with diarrhea and vomiting, without dehydration per WHO classification.[4,5] The primary outcome was the administration of isotonic fluid at equal to or greater than 20 mL/kg for rehydration within 72 hours of randomization. No significant difference was found in the percentage of children receiving intravenous fluids between the placebo (10.8%) and ondansetron (10.3%) groups (odds ratio [OR], 0.95; CI, 0.56–1.59) or in the secondary outcome of the presence of vomiting between groups, which was 24.0% in the placebo group and 19.6% in the ondansetron group (OR, 0.77; CI, 0.53–1.13). Six adverse events were reported in each group, none of them serious. The study was limited by inconsistent coadministration of other medications, including antibiotics and other antiemetics, which may have minimized the effect of ondansetron. More research needs to be done to confirm these findings, but this randomized control trial offers a strong argument against prescribing ondansetron for nondehydrated children presenting with vomiting and diarrhea.

In a systematic review with meta-analysis done to assess efficacy of ondansetron for vomiting in children with acute gastroenteritis, 10 randomized controlled trials (RCTs) involving 1,215 patients were reviewed.[2] Although ondansetron administration compared with placebo increased the chance of cessation of vomiting up to one hour after administration of the medication with a relative ratio (RR) of 1.49 (95% CI, 1.17–1.89), there was no difference between the groups after 4, 24, and 48 hours. Ondansetron use did reduce the risk of hospitalization (RR, 0.53; 95% CI, 0.29–0.97) and also reduced the need for IV hydration (RR, 0.45; 95% CI, 0.31–0.63). Presence of dehydration per WHO criteria was not uniform in these studies.

In a systemic review of randomized trials comparing antiemetic use to placebo in children with vomiting as a result of AGE, two trials totaling 181 participants were reviewed.[3] In one of the included trials, more patients who received ondansetron or metoclopramide had cessation of

TABLE. WHO tool for classifying dehydration[5]

Signs	Classification
Two of the following signs	Severe dehydration
Lethargy, loss of consciousness	
Sunken eyes	
Inability to drink properly	
Skin pinch returns very slowly (≥2 s)	
Two of the following signs	Some dehydration
Restlessness, irritability	
Sunken eyes	
Thirst	
Skin pinch returns slowly	
Not enough signs to classify as some or severe dehydration	No dehydration

vomiting in the following 24 hours than those who received placebo. In the second trial, eight of 12 patients (67%) who received ondansetron had complete cessation of emesis for the following four hours, and seven of 12 patients (58%) had cessation of vomiting for the following 24 hours.

CASE CONCLUSION

After reviewing the existing data, you share with your patient's mother that though ondansetron could help reduce emesis in her child, it is unlikely it would reduce the need for IV fluid if her child is maintaining hydration independently. EBP

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The authors declare no conflicts of interest.

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After an initial period of anticoagulation, are IVC filters better than no IVC filters in preventing recurrent pulmonary embolism?

EVIDENCE-BASED ANSWER

In patients who can be treated with anticoagulation, inferior vena cava (IVC) filters offer little-to-no help in preventing recurrent pulmonary embolism (PE) and may increase the risk of deep vein thrombosis (DVT) (SOR: **B**, based on inconsistent randomized controlled trials [RCTs]). Guidelines do not recommend IVC filters for use in patients who are adequately anticoagulated; however, clinicians might consider IVC filters for patients at high-risk for PE when anticoagulants are contraindicated or when a PE occurs in spite of adequate anticoagulation (SOR: **C**, expert opinion).

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A 2015 multicenter open-label RCT (N=399) from France compared anticoagulation to anticoagulation plus retrievable IVC filter to prevent recurrent PEs in high-risk patients.[1] Participants were hospitalized adults (mean age 73.4 years old; 51.9% female, 25.1% obese) with an acute symptomatic PE associated with lower-limb vein thrombosis; the PE was unprovoked in 76.7%. Patients had to have at least one additional risk factor for recurrence (eg, age >75 years, active cancer, chronic cardiac or respiratory insufficiency, ischemic stroke with leg paralysis within the previous 6 months, bilateral DVT or one that involved the iliocaval segment, right ventricular dysfunction, or myocardial injury). The study excluded patients with a contraindication to anticoagulation and those with recurrent thromboembolism while taking adequate anticoagulation. All patients received six months of anticoagulation with either a vitamin K antagonist (86%) or low-molecular-weight heparin (14%), and 200 were randomly selected to receive a retrievable IVC filter with the intent to remove it at three months. Filter placement was successful in 193 patients, and 180 were still alive at three months; of these, filter removal was contraindicated, unsuccessful, or refused in 27. Fatal or symptomatic PE recurrence was the primary outcome at three months and a secondary outcome at six months. There was no difference in the rate of PE recurrence between the filter and nonfilter groups at three months (3.0% and 1.5%, respectively, relative risk [RR] 2.0; 95% CI, 0.51–7.9) and at six months (3.5% and 2.0%, respectively, RR 1.8; 95% CI, 0.52–5.9). There were no differences between the two groups in terms of recurrent DVT, major bleeding, or mortality. The study was limited by a lower than expected rate of PE recurrence, leading to a potential underestimate of the sample size needed to show a statistically significant difference between groups.

A 1998 open-label RCT from 44 centers in France evaluated the efficacy of IVC filters for preventing PE in 400 patients with known proximal DVTs.[2] Patients were an average age of 72.5 years old, 52.5% were female patients, and 57% had a concomitant PE at baseline. All patients were given either unfractionated heparin or low-molecular-weight heparin, followed by warfarin or similar vitamin-K antagonist on day four, titrating the dose to maintain an international normalized ratio between two and three; 200 patients were randomly allocated to also receive a permanent IVC filter. The primary outcome was occurrence of a PE, either symptomatic or asymptomatic, within 12 days of randomization as assessed by pulmonary angiography or ventilation-perfusion scanning. Secondary outcomes included symptomatic PEs, DVTs, death, and major bleeding during two years of follow-up. There was a lower incidence of the primary outcome for patients who received IVC filter versus those who did not (1.1% vs 4.5%, respectively, odds ratio [OR] 0.2; 95% CI, 0.05–0.9). However, there were no differences in rates of secondary outcomes except for the incidence of recurrent DVT, which was higher among those with versus without IVC filters (20.8% vs 11.6%, respectively, OR 1.9; 95% CI, 1.1–3.2). The study was limited by the inability to recruit a planned enrollment of 800 patients in order to demonstrate a five-fold reduction in the incidence of PE in the intervention group.

A 2005 follow-up to the 1998 RCT[2] analyzed eight years of outcome data from 396 patients (99%).[3] At eight years, 198 were still alive (101 with IVC filters); of these, 50% from each group continued on vitamin K antagonists. One or more PEs occurred in 6.2% of the IVC filter group versus 15.1% of the nonfilter group (hazard ratio [HR] 0.37; 95% CI, 0.17–0.79); however, DVTs were more common in the IVC filter patients than in the nonfilter patients (35.7% vs 27.5%,

respectively, HR 1.5; 95% CI, 1.0–2.3). There were no differences in mortality, major bleeding, or postthrombotic syndrome between the two groups.

A 2016 evidence and consensus-based guideline from the American College of Chest Physicians recommended against using IVC filters for patients with acute DVT or PE who are treated with anticoagulants (grade 1B; strong recommendation based on moderate-quality evidence).[4] A 2019 evidence and consensus-based guideline from the European Society of Cardiology, in collaboration with the European Respiratory Society, also recommended against the routine use of IVC filters in the management of acute PE (general agreement that procedure is not beneficial and may be harmful, based on data from multiple RCTs). The guideline stated that IVC filters should be considered in patients with acute PEs and absolute contraindications to anticoagulation and in those who developed recurrent PEs despite adequate anticoagulation (consensus favors usefulness, based on expert opinion and case reports).[5] EBP

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Does the addition of misoprostol to the active management of the third stage of labor result in fewer postpartum hemorrhages?

EVIDENCE-BASED ANSWER

Yes. In the management of the third stage of labor, misoprostol reduces the incidence of 500 and 1,000 mL postpartum hemorrhages compared with placebo The addition of misoprostol to oxytocin reduces the incidence of 500 ml postpartum hemorrhages compared to oxytocin alone, but not 1,000 mL hemorrhages (SOR: A, meta-analysis). Misoprostol is considered a first-line medication for the management of postpartum hemorrhage due to uterine atony (SOR: C, expert opinion).

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A 2018 meta-analysis of 196 randomized controlled trials (RCTs) compared seven uterotonic drugs to placebo or no treatment during the third stage of labor for the prevention of postpartum hemorrhage (N=135,559).[1] The women studied had in-hospital (95%) vaginal births (72%) and 34% were high risk of for hemorrhage. Most trials included singleton pregnancies (63%) that did not specify parity. The majority of patients delivered at term. Primary outcomes included postpartum hemorrhage greater than or equal to 500 and 1,000 mL. Secondary outcomes included maternal deaths and severe maternal morbidity. Misoprostol was given at doses ranging from 50 to 1,000 μg administered orally, sublingually, rectally, or vaginally. Oxytocin was administered as either intramuscular (IM), IV bolus, IV infusion, IV bolus and infusion, or IM and IV infusion at doses ranging from 0.5 to 61 IU. Trials were excluded if medications were not given systemically, not administered immediately after birth, or if trials exclusively compared differing dosages, routes, or regimens of the same medication. Misoprostol

compared to placebo/no intervention was shown to prevent postpartum hemorrhage over 500 and 1,000 mL (7 trials, n=4,047; RR 0.63; 95% CI, 0.52–0.76 and 8 trials, n=5,467; RR 0.71; 95% CI, 0.59–0.85). Misoprostol in addition to oxytocin compared to oxytocin alone decreased postpartum hemorrhage over 500 mL but was no different in rates of hemorrhages over 1,000 mL (14 trials, n=8,148; RR 0.7; 95% CI, 0.58–0.86 and 17 trials, n=8,514; RR 0.88; 95% CI, 0.70–1.1). The addition of misoprostol to oxytocin decreased the use of further uterotonic drugs and rates of blood transfusions (18 trials, n=8,391; RR 0.56; 95% CI, 0.42–0.73 and 19 trials, n=8,742; RR 0.51; 95% CI, 0.37–0.70). Addition of misoprostol to oxytocin increased the risk of emesis (11 trials, n=6,718; risk ratio [RR] 2.1; 95% CI, 1.4–3.2) and pyrexia (17 trials, n=8,607; RR 3.1; 95% CI, 2.2–4.5). No difference was noted between doses of misoprostol. Misoprostol is not Food and Drug Administration approved for use in the prevention of postpartum hemorrhage.

A 2017 evidence-based practice guideline by the American College of Obstetricians and Gynecologists on the management of postpartum hemorrhage recommended that uterotonic drugs be the first-line intervention for uterine atony.[2] The guideline stated that the drug chosen should be left to the physician due to the lack of evidence for superiority of one drug over others (level A recommendation based on good and consistent scientific evidence). Medications listed as acceptable first-line drugs were oxytocin (10–40 U/500–1,000 mL as an infusion or 10 U intramuscular), methylergonovine (0.2 mg intra-muscular), 15-methyl $PGF_{2\alpha}$ (0.25 mg intramuscular or intramyometrial), and misoprostol (600–1,000 μg sublingual, oral, or rectal).

A 2018 evidence-based practice guideline by the Queensland Clinical Guidelines Committee gave recommendations on the prevention of postpartum hemorrhage.[3] These recommendations included massage of the uterus and emptying the bladder to be followed by first-line uterotonic drugs. The listed uterotonic drugs included oxytocin (5 U IV over 1–2 minutes or 5–10 U per hour infusion), ergometrine (not approved for use in the United States; 0.25 mg IV over 1 to 2 minutes or intramuscular), and misoprostol (800–1,000 μg per rectal). No strength of recommendation was provided. EBP

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In adults with COPD, does the addition of mucolytic agents decrease the likelihood of having an exacerbation?

EVIDENCE-BASED ANSWER

The use of a mucolytic agent in adult patients with chronic obstructive pulmonary disease results in a small reduction in the frequency of exacerbations (SOR: **A**, meta-analyses of randomized controlled trials [RCTs]). Both low and high doses of N-acetylcysteine are effective in reducing exacerbations (SOR: **A**, meta-analysis of RCTs).

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In 2019, a meta-analysis included 38 RCTs (N=10,377) examining mucolytic agents to decrease the frequency of exacerbations in adults with chronic obstructive pulmonary disease (COPD) of any severity.[1] Interventions included daily oral N-acetylcysteine (400–3,600 mg), carbocysteine, ambroxol, erdosteine, sobrerol, carbocysteine-sobrerol, carbocysteine-lysine, letosteine, cithiolone, iodinated glycerol, N-isobutyrylcysteine, Myrtol, and cineole with lysozyme. The duration of treatment in these trials varied between two months and three years. The patient population included male and female

adults older than 20 years old, with a mean age ranging from 40 to 71 years, and a diagnosis of COPD or chronic bronchitis of any severity. The percentage of smokers included in the primary studies varied between 55% and 100%. Primary outcomes included exacerbations and days of disability, and secondary outcomes included quality of life outcomes, mortality, and adverse events. An exacerbation was defined as an increase in cough with increased volume or purulence of sputum. Regular use of mucolytics reduced the likelihood of having an acute exacerbation when compared with a placebo (28 trials, n=6,723; Peto odds ratio (OR) 1.7; 95% CI 1.6–1.9; moderate certainty evidence; number needed to treat=8). Those prescribed a mucolytic had a reduction in disability days per month compared with the placebo (9 trials, n=2,259; mean difference –0.43 days per month; 95% CI –0.56 to –0.3). A decrease was observed in adverse effect between mucolytics and placebo (24 trials, n=7,264; OR 0.84, 95% CI 0.74–0.94). No difference was observed in the quality of life measures. Mortality benefit could not be determined because of the few numbers of deaths. Sources of potential bias in the primary studies were noted: not clearly describing allocation concealment, high attrition, and industry funding. Other limitations included heterogeneity of treatment types and the large span in time over which the primary studies were published.

A 2015 meta-analysis of 13 trials (12 RCTs and 1 cohort trial) looked specifically at the influence of different doses of N-acetylcysteine on COPD or chronic bronchitis exacerbations (N=4,155).[2] Although there is overlap in 12 of the 13 primary studies to the above meta-analysis, this study further explores the dose response relationship of a mucolytic. N-acetylcysteine was compared with the placebo for a duration between 4 and 36 months. The primary studies included patient populations of male and female adults with a mean age of 50 to 71 years old and included both smokers and nonsmokers. The daily dose of oral N-acetylcysteine varied from 200 to 1,200 mg, where a daily dose greater than 600 mg was considered high dose and 600 mg or less was considered low dose. Patients treated with N-acetylcysteine had significantly fewer exacerbations (relative risk [RR] 0.75, 95% CI 0.66–0.84). Both high and low doses of N-acetylcysteine reduced exacerbations (4 trials, n=1,997; RR 0.65, 95% CI 0.49–0.88 and 10 trials, n=2,912; RR 0.76, 95% CI 0.65–0.89.) N-acetylcysteine, regardless of dose, did not increase the risk of adverse events. One limitation of this analysis was that the primary studies used a variety of different definitions for an acute exacerbation of chronic bronchitis or COPD. EBP

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Does the MMRV vaccine increase the risk of seizure?

EVIDENCED-BASED ANSWER

The data are inconsistent. In children 9 to 24 months old, combined measles-mumps rubella-varicella (MMRV) vaccine compared to measles-mumps rubella and separate varicella vaccine (MMR+V) or measles-mumps rubella (MMR) showed no difference in seizure rates after the first and second vaccines (SOR: **A**, meta-analysis of clinical trials). However, postmarketing analysis in children 10 to 24 months found a moderately increased risk of febrile seizure comparing MMRV and MMR+V or MMR after the first vaccine, but no difference for children 4 to 6 years old with the MMRV and MMR+V for the second vaccine (SOR: **B**, meta-analysis of cohort and case control trials). The Advisory Committee on Immunization Practices recommends MMR+V for the first vaccine and MMRV for the second vaccine (SOR: **C**, guideline).

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A 2015 meta-analysis including 39 studies (31 clinical trials and 8 postmarketing observational safety surveillance studies) assessed the risk of febrile seizure after

measles-mumps rubella-varicella (MMRV) administration in over 3.2 million children (0 to 6 years old; multiethnic).[1] Studies included 30 randomized control trials, one non-randomized trail, seven cohort studies, and one self-controlled case series study. Vaccination series included: MMRV, measles-mumps rubella and separate varicella vaccine (MMR+V), measles-mumps rubella (MMR), and MMRV plus other childhood vaccines. Febrile seizure was defined as a seizure within the first 42 days after vaccination identified by International Classification of Disease-9 (ICD) or ICD-10 code, Brighton Collaboration criteria, Jacobsen criteria, chart review, or physician diagnosis. In children 9 to 24 months old, there was no difference in the rate of febrile seizure and vaccine-related febrile seizure at 0 to 42 days and 7 to 10 days between MMRV and MMR+V nor MMRV and MMR at the first and second doses. Subgroup analysis data from postmarketing observational studies showed a significantly higher risk of febrile seizures for children 10 to 24 months old at both 7 to 10 days and 5 to 12 days for the MMRV group compared to MMR+V (1 trial, n=not reported; risk ratio [RR] 2.04; 95% CI, 1.44–2.9 and 2 trials, n=not reported; RR 1.77; 95% CI, 1.08–2.91) and MMR (1 trial, n=not reported; RR 2.36; 95% CI, 1.03–5.38 and 2 trials, n=not reported; RR 2.32; 95% CI, 1.49–3.6). This was equivalent to one extra febrile seizure per 2,300 to 2,600 MMRV doses. Rates of febrile seizure were increased for children 10 to 24 months old at 0 to 42 days postvaccine for MMRV versus MMR+V (3 trials, n=not reported; RR 1.4; 95% CI, 1.1–1.7), but not for MMRV versus MMR (2 trials, n=not reported; RR 1.3; 95% CI, 0.98–1.7). There was no difference in rates of febrile seizure in children 4 to 6 years old at 7 to 10 days postvaccine for MMRV and MMR+V. Potential publication bias was noted.

In 2010, the Advisory Committee on Immunization Practices (ACIP) released recommendations for measles, mumps, rubella, and varicella vaccines.[2] The ACIP recommended MMR+V over MMRV for the first dose coverage in pediatric patients 12 to 47 months old should the parent have no preference. The ACIP expressed a general preference for MMRV for the second dose administration in patients 15 months to 12 years old. EBP

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Is the combination of a short-acting beta-agonist and muscarinic antagonist more effective than a short-acting beta-agonist alone in adults with asthma exacerbations?

EVIDENCE-BASED ANSWER

In patients presenting to the emergency department with acute asthma exacerbations, the addition of inhaled short-acting muscarinic antagonists to inhaled short-acting beta-agonists (SABAs) reduces the rate of hospitalizations in adults with severe exacerbations compared to treatment with SABAs alone (SOR: **A**, 2 meta-analyses of randomized controlled trials [RCTs]). Additionally, combination therapy is more effective in preventing hospitalizations for patients with severe exacerbations (SOR: **A**, meta-analysis of RCTs).

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A 2017 meta-analysis of 23 RCTs (N=2,724) compared the effectiveness of inhaled short-acting muscarinic antagonists (SAMAs) and short-acting beta-agonists (SABAs) to inhaled SABAs alone in patients presenting to emergency departments with an uncomplicated acute asthma exacerbation.[1] Patients

had a confirmed asthma diagnosis and were mostly over 18 years old (with 1 study beginning enrollment at 13 and another at 15 years old). The intervention groups were provided single or repeated doses of SAMAs and SABA agents or they received combination SABA/SAMA agents (eg, Duonebs). The control groups received only SABA agents either with or without a placebo. The most common SABA used was salbutamol (19 of 23 trials), and the most common SAMA used was ipratropium bromide (19 of 23 trials). Sixteen studies used nebulization of medication as the mode of delivery, while seven used metered dose inhalers. The primary outcome was hospitalization rates in patients presenting to the Emergency Department with acute asthma exacerbation. Overall, patients who received combination therapy of inhaled SABAs and SAMAs were less likely to be hospitalized compared to participants who received SABAs alone (16 trials, n=2,120; risk ratio [RR] 0.72; 95% CI, 0.59–0.87, number needed to treat 16). In particular, combination therapy was more effective at reducing hospitalization rates in patients with severe asthma exacerbations compared to SABA therapy alone (7 trials, n=599; RR 0.56; 95% CI, 0.43–0.72), but there were no significant differences found between the two treatments in subgroup analyses of individuals with moderate or mild asthma exacerbations or populations at lower risk of hospitalization. Adverse events including but not limited to dry mouth, nausea, palpitations, and tremors were higher in the SAMA/SABA therapy group compared to the SABA group, but these were not severe (11 trials; n=1,392; odds ratio 2.03; 95% CI, 1.28–3.20).

A 2005 meta-analysis (N=3,611) of 32 randomized and placebo-controlled trials with the similar goal of evaluating efficacy of combination SAMA/SABA treatment in comparison to SABA treatment in reducing hospitalizations.[2] The intervention groups received single or repeated doses of inhaled anticholinergics (ipratropium bromide in 29 of 32 trials) with SABAs (salbutamol), while the control groups received SABAs alone. A subanalysis of 16 trials (n=2,047) only examining adults was identified. Eight trials used a single dosing protocol, and the other eight used a multiple dose protocol. The severity of asthma exacerbation was classified by clinical score or the spirometric measurements forced expiratory volume in one second and peak expiratory flow, where 50% to 70% of expected values was classified as moderate exacerbation and less than 50% of expected values as severe exacerbation. Adult patients who received combination therapy had significant reductions in hospital admissions compared to SABA treatment alone (9 trials, n=1,556; RR 0.68; 95% CI, 0.53–0.86). EBP

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In adults with adhesive capsulitis, are surgical interventions effective at relieving pain and improving function?

EVIDENCE-BASED ANSWER

Arthroscopic capsular release (ACR) in adult patients with idiopathic adhesive capsulitis (AC) moderately improves the range of motion but not pain or functional scores compared with ACR in patients with AC associated with diabetes (SOR: **B**, systematic review of comparative case series studies). There seems to be no significant difference in the outcomes when comparing ACR and manipulation under anesthesia (SOR: **A**, systematic review of comparative case series and retrospective cohort studies).

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A 2019 systematic review of six comparative case series studies (N=463) evaluated preoperative and

postoperative functional and pain-related outcomes in patients with adhesive capsulitis (AC) after arthroscopic capsular release (ACR).[1] The studies included adults (mean ages 48–56) with specific underlying etiologies, listed below, treated for ACR not responsive to conservative therapy including but not limited to physical therapy, exercise program, or manipulation. The patients were classified as having primary or secondary AC. Primary AC included 61 diabetic patient cases and 203 patients diagnosed with idiopathic AC. Secondary AC included 69 posttraumatic, 100 postsurgical, and 30 degenerative cases. The primary outcome was shoulder range of motion (ROM, most commonly shoulder flexion, external rotation, and internal rotation). The secondary outcomes included assessment of Activities of Daily Living (ADLs) and pain using the Constant-Murley (CM) score (scale 0–100) or the American Shoulder and Elbow Score (ASES), visual analog sores (VAS), and complications/revision procedure rates. The mean follow-up times ranged from 1 to 4.5 years. A subset of studies included diabetic patients (4 trials, n=61 of 175 total patients). Diabetic patients demonstrated less active external rotation (1 trial, n=68; 44° vs 58°, *P*=.004) and a lower mean degree of forward flexion and external rotation at six months (1 trial, n=37; forward flexion 152° vs 162°, *P*=.045; external rotation 43° vs 55°, *P*=.021) compared with idiopathic cases post-ACR. Treatment with ACR resulted in higher postoperative CM mean scores in idiopathic patients compared with diabetic patients (n=28, 82 vs 94, *P*<.05, mean follow-up time 54 months; n=42, 67 vs 80, *P*<.01, at 6 months). The other two studies did not include diabetic patients and found no significant differences in CM scores between idiopathic and secondary cases. Of the four studies that included diabetic patients, one reported a difference in pain at the final follow-up between the diabetic and idiopathic groups (n=15 of 56, 26% of diabetic patients vs 0% of idiopathic patients), although this was not statistically significant. Comparison of idiopathic and secondary cases did not demonstrate any significant differences in ROM, CM score, ASES, pain, or VAS. Limitations include significant heterogeneity in outcome measures between studies.

Conservative therapy for AC generally involves physical therapy and office-based manipulation of the affected shoulder. If a patient fails conservative treatment, a surgeon may recommend manipulation under anesthesia (MUA) or ACR. A 2013 systematic review of 22 studies including 18 case series and four cohort studies (N=989) examined clinical outcomes after MUA or ACR for the treatment of AC.[2] The trials included adult patients (median age 52) diagnosed with either idiopathic or secondary AC who did not improve with conservative therapy. The preintervention and postintervention outcomes of ROM (including abduction, forward elevation, and external rotation at the side [ERS]) and patient-oriented secondary outcome scores, of which the CM score was the only outcome reported in multiple studies evaluating MUA, were assessed with a mean follow-up time of 33 months. The outcomes were reported as a median change or median score. A change in the CM score of 10 units or a change in ROM of 10° or greater was considered clinically significant. Treatment with ACR minimally improved abduction (ACR: median change 89°, 8 patient cohorts, n=186; MUA: median change 83°, 3 patient cohorts, n=218, *P* value not reported) and ERS (ACR: median change 47°, 13 patient cohorts, n=472; MUA: median change 40°, 4 patient cohorts, n=276, *P* value not reported). In a comparison of one MUA cohort and three ACR cohorts, treatment with ACR resulted in a 12% higher median CM score compared with treatment with MUA. Treatment with ACR also resulted in a higher overall complication rate, including superficial wound infection, proximal humerus fracture, and diffuse brachial plexopathy (15 patient cohorts, n=638; 0.6% vs 0.4%) compared with MUA. Limitations include heterogeneity in the ROM measurements and patient-oriented secondary outcome measurements, and cohort sizes are too small to directly compare ACR and MUA. EBP

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In patients undergoing ambulatory, medically supervised alcohol withdrawal, is gabapentin or a benzodiazepine more effective in alleviating symptoms of withdrawal and preventing worsening symptoms?

EVIDENCE-BASED ANSWER

In adults withdrawing from alcohol in the outpatient setting, gabapentin is probably more effective than benzodiazepines in controlling alcohol withdrawal symptoms (SOR: **C**, conflicting evidence from 2 small randomized controlled trials [RCTs]). Gabapentin additionally produces less daytime sleepiness than benzodiazepines (SOR: **C**, small RCT) and may decrease alcohol cravings, anxiety, and relapse during treatment compared with benzodiazepines (SOR: **C**, small RCT).

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A 2013 randomized doubled-blind head-to-head study (N=26) compared gabapentin with chlordiazepoxide in managing alcohol withdrawal symptoms.[1] Participants were U.S. veterans (25 male and 1 female with mean age of 53 years old) diagnosed with alcohol withdrawal via Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria. Exclusion criteria included those requiring hospitalization or taking benzodiazepines or nonbenzodiazepine anticonvulsants. Participants also could not participate with any major psychiatric condition requiring emergency management or if they met criteria for comorbid benzodiazepine, opioid, or barbiturate abuse/dependence. Patients assigned to the gabapentin group (n=17) were dosed initially at 1,200 mg, and then 900 mg on day four, 600 mg on day five, and 300 mg on day six. Patients in the chlordiazepoxide group (n=9) were dosed at 100 mg on days 1 to 3, 75 mg on day four, 50 mg on day five, and 25 mg on day six. Each patient also received a placebo that was similar visually to the study medications. Only 11 of 17 participants in the gabapentin group and six of nine in the chlordiazepoxide group completed the study. Outcomes measured were clinical withdrawal symptoms, daytime sleepiness, and alcohol cravings. Evaluation was performed on days four and seven using the Clinical Institute Withdrawal Assessment for Alcohol revised (CIWA-Ar; scale 0–67, with higher score indicating more withdrawal symptoms), Epworth Daytime Sleepiness Scale (scale 0–24, with higher score indicating more sleepiness), and the Penn Alcohol Craving Scale (PACS; scale 0–30, with higher score indicating increased craving). There were no significant differences between treatment groups on day four in any of the measurements. On day seven, gabapentin demonstrated lower levels of daytime sleepiness compared with chlordiazepoxide (mean difference –3.70; 95% CI, –7.21 to –0.19) but no differences in PACS or CIWA-Ar scores.

A 2009 randomized controlled trial (N=100) evaluated the efficacy of gabapentin versus lorazepam for the management of alcohol withdrawal in an ambulatory setting.[2] Participants were 77% male and mean age was 39 years old. Patients were included with a DSM-IV diagnosis of alcohol dependence with withdrawal evidenced by CIWA-Ar score of 10 or greater, a Mini-Mental Status Examination (range 0–30, higher scores indicating higher mental functioning) score of 26 or greater, and blood alcohol level of 0.1 g/dL or less. Gabapentin (n=72) was dosed at 1,200 mg daily tapered to 900 mg daily over four days, 900 mg daily tapered to 600 mg daily over four days, or 600 mg daily. The 600 mg treatment group (n=16) was discontinued after two patients reported medically unwitnessed seizure-like episodes and one subject had a near syncopal event. Lorazepam (n=28) was dosed at 6 mg daily tapered to 4 mg daily over four days. The primary outcome was alcohol withdrawal symptoms measured with CIWA-Ar on days 1 to 5, 7, and 12. Secondary outcomes included alcohol cravings that were measured with a 0- to 100-point visual analog scale, with higher scores indicating increased cravings and anxiety levels measured by the Zung Anxiety Scale (range 20–100 with higher score representing increased anxiety). Relapse rates were also assessed during the study using breath alcohol tests and verbal reports. Overall, alcohol withdrawal symptoms decreased over time in all groups. Alcohol withdrawal symptoms during the treatment phase were not significantly different between low-dose gabapentin (n=28) and lorazepam group (4.5 vs 4.3,

P=.62) but symptoms were significantly improved when using high-dose gabapentin (n=28) compared with lorazepam (3.1 vs 4.3, P=.03). The difference in withdrawal symptoms between high-dose gabapentin and lorazepam was even more significant during the follow-up phase (1.0 vs 2.5, P=.01). The combined gabapentin group also had less probability of relapse after day one (9% vs 27%, P=.027 on day 2; 8% vs 40%, $P<.01$ on day 6), as well as less reported cravings (29 vs 42, $P<.05$) and decreased anxiety (32 vs 37, $P < .05$) compared with lorazepam during the treatment phase. A limitation of this study is a small sample size because of high dropout rates, making statistical significance difficult. EBP

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Are omega-3 fatty acids effective in the treatment of children with ADHD?

EVIDENCE-BASED ANSWER

Perhaps. There may be small improvements in symptoms of attention deficit hyperactivity disorder (ADHD) with omega-3 fatty acid supplementation (SOR: **C,** conflicting evidence from a meta-analysis of of randomized controlled trials [RCTs] and 2 single RCTs).

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A 2011 meta-analysis of 10 RCTs (n=699) assessed the effect of omega-3 fatty acid supplementation with alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), or docosahexaenoic acid (DHA) in children with ADHD compared to placebo.[1] Children with both diagnosed ADHD or symptoms of ADHD were included with most trials having a mean age of around 9 to 10 years old. Children were excluded if they were started on any other psychoactive medications at the same time as the trial medications. Eight trials examined EPA (dose range, 80–750 mg), nine trials examined DHA (dose range, 2.7–480 mg), and only three trials examined ALA (dose range, 1–120 mg). Most trials used either olive oil or canola oil as placebo. Trial duration lasted between seven weeks and four months, with most trials lasting three months. Due to heterogeneity in ADHD scoring scales used, results were pooled and converted to standardized mean differences (SMDs). After pooling all 10 trials, omega-3 fatty supplementation had a small positive effect on clinical rating scales measuring ADHD severity compared to children on placebo (SMD 0.31; 95% CI, 0.16–0.47). Omega-3 fatty acid supplementation was similarly effective on inattentive symptoms (SMD 0.29; 95% CI, 0.07–0.50) and hyperactivity symptoms (SMD 0.23; 95% CI, 0.07–0.40) compared to placebo.

A 2008 double blinded RCT (n=129) compared polyunsaturated fatty acid (PUFA) supplementation versus placebo on ADHD symptoms and markers of cognition.[2] Children included were aged 7 to 12 years old, had a diagnosis of ADHD by symptoms, and had not received either stimulants or PUFA supplementation in the preceding three months. Participants were excluded if they had a history of stimulant use. Children were randomized to take six capsules daily PUFA supplementation (400 mg fish oil, 100 mg primrose oil) plus a multivitamin (n=46) versus six capsules daily of PUFA supplementation alone (n=45) versus six capsules of palm oil placebo (n=38) for 16 weeks. Main outcomes measured were overall ADHD symptom improvement measured by the Conners parent ADHD index, and improvement in controlling attention measured by the creature counting test. All outcomes were standardized into effect sizes (ESs). Children in both PUFA arms combined vs placebo showed a significant, small increase in ability to switch and control attention (ES 0.43, $P<.05$). There was a small improvement in Conners parent ADHD index at 15 weeks (ES 0.067, $P<.05$), but this small improvement is not considered to be clinically relevant. Limitations included lack of intention to treat in the analysis and small study size.

A 2014 double-blind RCT (n=95) examined the effect of omega-3 fatty acid supplementation on behavioral symptoms and cognitive impairment in children aged 6 to 12 years old diagnosed with ADHD via Diagnostic and Statistical Manual of Mental Disorders—fourth edition.[3] Children were excluded if they possessed an intelligence quotient of less than 70 and used stimulants or other psychoactive medications within the preceding six months. For 16 weeks, the treatment group was randomized to receive a total of 720 mg fatty acids daily (EPA 600 mg, DHA 120 mg) along with 15 mg vitamin E as an antioxidant (n=46) and the placebo group received a capsule containing olive oil (n=49). Results were converted into Z scores to evaluate if there was a significant difference from the mean. No difference was found between baseline and follow-up parent-rated symptoms using the Diagnostic System for Mental Disorders in Childhood and Adolescence (DISYPS-II) questionnaire in the supplement group compared to the placebo group ($Z=-0.65$, $P=.52$) nor was there a difference found between baseline and follow-up on the parent rating Child Behavior Checklist ($Z=-0.02$, $P=.98$). Teacher-rated symptoms were evaluated using the DISYPS-II questionnaire and the Teacher Report Form (TRF) and neither found a difference in ratings (DISYPS-II $Z=-0.2$, $P=.84$ and TRF $Z=-0.49$, $P=.62$). EBP

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Does inpatient treatment result in higher rates of remission than outpatient treatment of anorexia nervosa?

EVIDENCE-BASED ANSWER

There is no difference in remission rates between outpatient and inpatient treatment for anorexia nervosa (SOR: **B**, meta-analysis of randomized controlled trials). The Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines recommend a trial of outpatient therapy as first-line treatment for anorexia in adolescents (SOR: **C**, consensus guidelines).

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A 2019 meta-analysis of five randomized controlled trials compared treatment of anorexia nervosa (N=511) and bulimia (N=55) in multiple settings.[1] Three studies included patients 12 to 18 years old and one included adults. The Diagnostic and Statistical Manual of Mental Disorders IV criteria were used for the diagnosis of anorexia nervosa. The trials compared weight restoration after treatment for anorexia nervosa in the setting of three weeks of inpatient hospitalization versus active outpatient treatment (individual and group psychotherapy sessions, dietary counseling, cognitive behavioral treatment, or generic outpatient care from a provider not specialized in eating disorders) or outpatient treatment (occasionally with brief hospitalizations). Primary outcomes included weight or body mass index (BMI) and number of patients

completing the treatment. Secondary outcomes included weight restoration, recovery, and remission (defined as restoration of body mass index from 19 to 25 kg/mg^2 or >85% of the expected height and age at the end of 12 months from the onset of treatment or 2 years after initial weight baseline). For anorexia nervosa, no difference was found in weight gain, BMI, or restoration of weight within the normal range when comparing inpatient to active outpatient or combined brief hospitalization-outpatient treatment (3 trials, n=232; standardized mean difference –0.22; 95% CI, –0.49 to 0.05 and 1 trial, n=82; risk ratio [RR], 1.1; 95% CI, 0.65–1.7). Patients were less likely to complete inpatient treatment compared with specialist outpatient treatment (2 studies, n=154; RR, 0.72; 95% CI, 0.52–0.86), but there was no difference between inpatient and nonspecialist outpatient treatment. Similarly, there was no difference in weight restoration between inpatient care and nonspecialist's outpatient care or specialist outpatient care (1 trial, n=101; mean difference, –3.7 kg; 95% CI –8.96 to 1.5). Although there was no overt difference in levels of remission between settings, remission rates in general were in the expected range of > 50%, which is comparable to other studies regarding treatment of anorexia nervosa. The quality of evidence in all trials was downgraded as a result of the risk of bias, lack of blinding, and the variations in specialists' knowledge and level of treatment.

The Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines issued guidelines in 2014 concerning the recommended treatment of eating disorders, including anorexia nervosa.[2] These guidelines were developed by an expert panel based on a comprehensive literature review and evaluated using the National Health and Medical Research Council criteria. The guidelines recommended outpatient treatment as first line in adolescent anorexia nervosa. These guidelines did not address the adult age group. EBP

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How effective is vaccination for preventing influenza in healthy children?

EVIDENCE-BASED ANSWER

In healthy children aged 2 to 17 years old, influenza vaccinations of any dose or type are effective in preventing influenza or influenza-like illnesses compared with placebo or no intervention (SOR: **A**, meta-analysis of randomized controlled trials [RCTs], single cohort, and a case-control study). Live attenuated vaccine can reduce influenza infection from 18% without vaccine down to 4% in children 2 to 16 years old, whereas inactivated vaccines can reduce the risk from 30% without vaccine down to 11% (SOR: **A**, meta-analysis of RCTs). There is no difference in effectiveness between one and two dose regimens (SOR: **C**, single case-control study).

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A 2018 systematic review and meta-analysis of 41 RCTs, 19 cohort studies, and 11 case-control studies assessed the efficacy and effectiveness of influenza vaccines versus placebo or no intervention to naturally occurring influenza in over 200,000 healthy children.[1] Participants in the study were healthy and between the ages of 2 and 16 years old. Vaccination with any influenza vaccine in any dose, preparation, or time schedule was compared with placebo or no intervention. Outcomes measured included reported influenza symptoms with a positive laboratory diagnosis or influenza-like illness (ILI) symptoms (headache, high temperature, cough, and muscle pain). Live attenuated influenza vaccines compared with placebo or no intervention significantly reduced influenza infection from 18% down to

4% (7 RCTs, n=7,718; risk ratio [RR] 0.22; 95% CI, 0.11–0.41) and reduced ILI risk from 17% to 12% (7 RCTs, n=124,606; RR 0.69; 95% CI, 0.60–0.80). Inactivated vaccines compared with placebo or no intervention significantly reduced the risk from 30% to 11% (5 RCTs, n=1,628; RR 0.36; 95% CI, 0.28–0.48) and reduced ILI from 28% to 20% (4 RCTs, n=19,044; RR 0.72; 95% CI, 0.65–0.79). Adverse event data were not well-documented or standardized across studies and conclusions could not be drawn for potential harms.

A 2019 interim prospective cohort study (N=3,254) evaluated influenza vaccine effectiveness in children and adults enrolled in the U.S. Influenza Vaccine Effectiveness Network.[2] Vaccine effectiveness was compared against no vaccination for all influenza virus infections associated with medically attended acute respiratory illness. Participants included both children (over 6 months old) and adults eligible for vaccination, who were reporting an acute respiratory illness with cough for less than seven days and had not been treated with influenza antiviral medication during their illness. Interventions included any self-reported or documentation of at least one dose of influenza vaccination (vaccine type not specified) greater than 14 days before onset of acute respiratory illness and were compared with those without vaccination. In a subanalysis of only children 6 months to 17 years old (n=1,099), relative vaccine effectiveness was 61% (95% CI, 44–73%). Limitations included variation in attack rate among age groups, geographic differences in circulating viruses, and genetic variation within virus subtypes.

A 2018 test-negative case-control study (N=20,033) analyzed data from five different studies in Japan over five consecutive influenza seasons from 2013 to 2018 to evaluate the effectiveness of the inactivated influenza vaccine by number of doses.[3] Participants included 20,033 children 6 months to 12 years old who had a fever greater than or equal to 38°C (100.6°F) and had received a rapid influenza diagnostic test in outpatient clinics of 24 hospitals. Vaccine effectiveness was analyzed by various dosing levels (no dose, 1 dose, 2 dose) and compared with rapid influenza diagnostic test-negative patients. In total, 10,897 children were unvaccinated, 1,956 were vaccinated once, and 7,180 were vaccinated twice. One dose of the inactivated influenza vaccine significantly reduced ILI and hospitalization for children over five consecutive seasons (odds ratio [OR] 0.56; 95% CI, 0.52–0.62) as did two doses (OR 0.55; 95% CI, 0.52–0.59) compared with children receiving no doses. There was no significant difference between one- and two-dose vaccinations (OR 1.01; 95% CI, 0.91–1.1). Limitations included reliance on rapid influenza diagnostic tests as compared with polymerase chain reaction and geographic variations in viral strains. EBP

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In pregnant women, does receiving the influenza vaccine reduce the risk of developing laboratory-confirmed influenza?

EVIDENCE-BASED ANSWER

Yes. Administration of influenza vaccinations in pregnant women reduces the risk of laboratory-confirmed influenza infection by about 53% (SOR: **A**, meta-analysis of randomized controlled trials, cohort studies, and case-control studies). The American College of Obstetrics and Gynecology (ACOG) states that influenza vaccination is an essential part of prenatal care (SOR: **C**, expert opinion).

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A 2019 meta-analysis of five randomized controlled trials (RCTs; n=10,463) and 14 observational studies (12 cohort studies, and 2 case-control studies, n=210,304)

evaluated the efficacy and effectiveness of the influenza vaccine in pregnant women.[1] Study populations were pregnant women from South Africa, Mali, Nepal, United States, Norway, and Australia. The RCT intervention groups received the trivalent inactivated influenza vaccine, whereas the control groups received placebo, or, in one RCT, the quadrivalent meningococcal conjugate vaccine. The primary outcome was incidence of laboratory-confirmed influenza infection. Influenza vaccination administration reduced the incidence of laboratory-confirmed influenza infection by 53% compared with placebo or meningococcal conjugate vaccine (3 RCTs, n=10,123; risk ratio [RR], 0.47; 95% CI, 0.31–0.71). Two case-control studies compared rates of laboratory-confirmed influenza infection in vaccinated versus unvaccinated pregnant women. Pooled analysis of these case control studies demonstrated a reduction in the incidence of laboratory-confirmed influenza infection in vaccinated pregnant women by 63% (2 case controls, n=364; RR, 0.37; 95% CI, 0.23–0.61). Side effects of the influenza vaccination were not reported in the meta-analysis. Limitations of this study included methodological heterogeneity in pooled estimate calculations, lack of reporting the timing of vaccination both in seasonality and gestational progression, and no report on how closely matched the vaccine was to the circulating strains.

In 2018, the ACOG released a committee opinion regarding the use of influenza vaccines during pregnancy.[2] The evidence-based recommendations were released in 2018 and reaffirmed in 2019. Regarding efficacy, ACOG stated that the effect of the influenza vaccine in pregnant women was similar to that of the general population. ACOG called the administration of the influenza vaccine an "essential" part of a woman's prenatal care. ACOG recommended that "all women who are or will be pregnant during influenza season receive an inactivated influenza vaccine as soon as it is available" (no level/grade of recommendation provided). EBP

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When should breastfed neonates with inappropriate weight gain be given supplemental formula?

EVIDENCE-BASED ANSWER

A weight loss nomogram based on delivery method can be used to identify infants at risk for inappropriate weight loss (SOR: **B**, single large cohort study). Healthy, term, exclusively breastfed infants may lose 7% to 10% of birth weight (SOR: **B**, single large cohort). Infants with weight loss ≥10% should not routinely be given supplemental formula for weight gain before having a breastfeeding evaluation and excluding medical causes (SOR **C**, consensus guideline).

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A weight loss nomogram for exclusively breast-fed infants was developed in 2015 to demonstrate typical neonatal weight loss trends in the first 72 to 96 hours of life.[1] The study was based on a retrospective case-control cohort of 108,907 infants from 2009 to 2013 in Northern California Kaiser Permanente hospitals. Inclusion criteria were healthy infants born via vaginal or cesarean delivery between 36 and 43 weeks' gestation, and birth weight >2,000 and <5,000 g. Infants with missing data points, multiple gestation, infectious or congenital disease, or who received level II or III neonatal intensive care unit care were excluded from the study. Vaginal deliveries totaled 76% (83,433) with an average of 2.3 weight measurements and cesarean deliveries totaled 23.4% (25,474) with an average of 3.1 weight measurements. At 48 hours, the median weight loss for vaginal delivery was 7.1% and cesarean delivery was 8.0%. By 72 hours of life, 5% of vaginally delivered infants lost >10% of birth weight and 25% of cesarean delivery infants lost >10% of birth weight. Nomograms

were created that demonstrate anticipated weight loss by percentile over 72 hours (vaginal delivery) or 96 hours (cesarean delivery). Important limitations of the study included nonstandardized scales, lack of information about why formula was initiated, and the time frame that weights had been recorded may not catch the actual weight nadir for all infants.

In 2003, a prospective observational cohort study of 937 term newborns >37 weeks' gestation with birth weights of ≥2,500 g who were breastfed (BF, n=420, 45%), formula fed (FF, n=396, 42%), or mixed fed (n=121, 13%) were followed for up to 21 days to determine maximal weight loss, timing of maximal weight loss, and time at which birth weight was regained.[2] Maximal weight loss differed significantly by feeding method at the 95th percentile for BF (–11.8%; 95% CI, 11.2–12.9) and FF (–8.4%; CI, 7.8–8.9) as well as the 97.5th percentile for BF (–12.8%; CI, 12.1–13.7) and FF (–9.5%; CI, 8.6–10.9). Weight loss nadir was 2.7 days for both groups. Median recovery of birth weight was 8.3 days for BF (as long as 18.7 days at the 95th percentile) and 6.5 days for FF (as long as 14.5 days at the 95th percentile). Authors recommended evaluation for other etiologies of weight loss if a FF infant had >10% weight loss or failed to regain birth weight by two weeks of life. Biochemical testing for dehydration was recommended for BF or FF infants with ≥12.5% weight loss or for failure to regain birth weight by three weeks.

In 2017, the Academy of Breastfeeding Medicine (ABM) released revised evidence-based guidelines, which recommend supplemental feeding with formula to neonates only in certain situations.[3] Infant indications for supplemental formula feeding included asymptomatic hypoglycemia, significant dehydration, delayed bowel movements, and hyperbilirubinemia. Maternal indications included delayed milk production, lactation failure, breast pathology, chemotherapy, or intolerable pain. The guidelines stated that healthy BF infants may lose 8% to 10% of their birth weight and that as long as an infant urinated and stooled appropriately and the physical examination was normal, the ABM did not recommend formula supplemented feeds. EBP

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Are trigger point injections with anesthetic (wet needling) more effective than trigger point injections without anesthetic (dry needling) in treating patients with myofascial pain?

EVIDENCE-BASED ANSWER

In general, the use of anesthetic (wet needling) compared with dry needling results in greater pain relief at 9 to 28 days, but not at 0 to 3 days or 2 to 6 months (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). In older adults, trigger point injections with anesthetic may be superior to dry needling for myofascial pain, with pain relief, higher patient satisfaction, and less discomfort during treatment (SOR: **C**, small RCT).

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A 2015 meta-analysis of 20 randomized controlled trials (RCTs; N=839) evaluated the effectiveness of needling myofascial trigger points associated with neck and shoulder pain.[1] Patients were 69% female and average mean age ranged from 30 to 79 years old. The studies included patients with myofascial pain with an

average duration of 22 months (range 2.1–64 months). The meta-analysis compared control (no intervention), dry needling, and wet needling (injecting lidocaine) with outcomes at 0 to 3 days (short term), 9 to 28 days (medium term), and 2 to 6 months (long term). Outcome measures included numerical pain score and a visual analog scale from 0 to 10 (higher number indicating greater pain). Dry needling had a large effect compared with control in the short term (6 trials, n=219; standard mean difference [SMD] –1.9; 95% CI, –3.1 to –0.73) and medium term (6 trials, n=257; SMD –1.1; 95% CI, –1.9 to –0.27) but not in the long term (2 trials, n=55; SMD 1.2; 95% CI, –3.3 to 1). Patients treated with dry needling had a large increase in pain compared with wet needling in the medium term (4 trials, n=180; SMD 1.7; 95% CI, 0.40–2.98), but no differences were observed in the short term (6 trials, n=208; SMD 0.01; 95% CI, –0.41 to 0.40) or long term (1 trial, n=80; SMD 0.33; 95% CI, –0.11 to 0.78). The main study limitations of this meta-analysis were the high heterogenicity because of the variation of the study designs, inclusion/exclusion criteria, difference in subjects, various outcome measures, and treatment differences.

A 2019 RCT (N=40) examined the efficacy of trigger point injections with lidocaine (wet needling) in treatment of geriatric individuals with myofascial pain compared with dry needling.[2] Patients over 60 years old with at least a three-month history of trigger point pain in their neck or shoulder region and a normal cervical computerized tomography or magnetic resonance imaging were included. The study excluded patients with underlying neurologic deficits, history of neck or shoulder surgery, or who were receiving any other pain treatment modality. For dry needling, a 25-gauge 1.5″ needle was inserted 1 to 2 cm from trigger point at an angle of 30° to the skin until twitch response occurred. Then the needle was introduced several times into the myofascial trigger point. For wet needling, 2 mL of 0.5% lidocaine was injected to the myofascial trigger point once muscle twitch occurred. Patient measures included pain score with a visual analog scale from 0 to 10 (with higher number indicating more severe pain), patient satisfaction (satisfied or unsatisfied), and patient discomfort. These measures were taken before intervention and two weeks posttreatment in each group. A significant decrease was noted in pain scores for wet needling before and after treatment (7.4 vs 2.8; $P<.001$). No difference was noted in pain with dry needling before and after treatment (7.0 vs 6.1; $P=.436$). Wet needling with lidocaine was superior to dry needling at two weeks for pain relief (2.8 vs 6.1; $P=.001$), less discomfort during treatment (20% of patients with discomfort during treatment vs 60%; $P=.009$), and overall better patient satisfaction (75% vs 40%; $P=.002$). The authors did not indicate what amount of change was needed to determine clinical significance. This RCT was limited because of the low number of participants, treatment of a single trigger point site, and only studied geriatric population. EBP

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Is physical therapy effective treatment of patellofemoral osteoarthritis?

EVIDENCE-BASED ANSWER

In patients with patellofemoral osteoarthritis, no improvement is noted in quality of life with nonsurgical treatment options (bracing or manual therapy) compared with education alone (SOR: **B**, meta-analysis of cross-sectional and interventional studies). Both physical therapy with squatting and physical therapy with squatting plus hip adduction may relieve pain and improve function similarly in patients with patellofemoral osteoarthritis (SOR: **C**, small randomized control trial).

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A 2018 meta-analysis of 17 studies (7 cross-sectional, 10 intervention studies of unclear design) in adults (N=2,650) with patellofemoral osteoarthritis compared

surgical, nonsurgical, and control groups for effect on quality of life.[1] Patients were between 18 and 83 years old, average age of 50 years old, 34% female, and mostly normal body mass index (average 27 kg/m^2) with some in the overweight and obese categories. Patients with patellofemoral osteoarthritis were compared in surgical (eg, matrix-induced autologous chondrocyte implantation, multipotent stem cells implantation), nonsurgical (eg, bracing, manual therapy), and control groups (education alone). Results were based on a Knee Injury and Osteoarthritis Outcome Score—Quality of Life score. Nonsurgical groups did not improve knee-related quality of life compared with control groups (3 studies, N=176; standardized mean difference 0.21; 95% CI, –0.02 to 0.45; I^2=0%). The effects of surgical treatment versus control group were not studied. Radiographic severity and other comorbidities were not considered in determining quality of life. Publication bias may have resulted in over estimation of effect sizes.

A 2019 randomized control trial examined the effectiveness of squatting compared with squatting and hip adduction rehabilitation in management of patellofemoral osteoarthritis in adult females (N=30).[2] Patients had anterior or retropatellar knee pain aggravated by at least two activities that loaded the patellofemoral joint most of the days of the month. Ages ranged between 35 and 50 years old, average age 37 years old. Patients were excluded if they had a prior history of hip or knee fractures, knee injections within three months, major knee surgery (not including arthroscopy), and patients with a Kellgren-Lawrence (a radiographic grading scale of osteoarthritis) of two or more from posteroanterior radiographs. One group received traditional physical therapy in addition to a squatting exercise program for four weeks. The second group received traditional therapy in addition to squatting plus hip adduction exercises for four weeks. The primary outcome measures were pain and performance of functional activities by the Kujala scale. The Kujala scale is a 13-question scale ranging from 0 to 100, with 0 indicating the highest disability. Pain intensity was measured on a numerical rating scale from 0 to 10 points (no pain to the worst pain possible). In the traditional physical therapy group, pain relieved and function improved from pretreatment to posttreatment (7 vs 2, $P<.0001$; and 58 vs 84, $P<.0001$). For squatting with hip adduction physical therapy group, patients' pain relieved and function also improved from pretreatment to posttreatment (7 vs 1, $P<.0001$; and 63 vs 88, $P<.0001$.) However, no significant differences were noted comparing traditional physical therapy with physical therapy plus squatting with hip adduction in pain or function (2 vs 1, $P=.051$; and 84 vs 88, $P=.41$). Limitations included differences between exercise groups instructions and some participants being limited by discomfort. Only 30 participants completed the entire study, which could lead to small sample size bias. EBP

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Is increased sleep duration effective for weight loss?

EVIDENCE-BASED ANSWER

Increased sleep duration is associated with small amounts of weight loss (SOR: **B**, meta-analysis of randomized controlled trials). Sleep durations greater than six hours compared to less than six hours per night is associated with better success with weight loss, reducing body mass indexes by an additional 3 to 5 kg/m^2 (SOR: **B**, cohort trial).

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A 2015 meta-analysis of 16 randomized controlled trials (RCTs; N=728) examined the effect of sleep duration on body weight and energy balance.[1] Four studies evaluated the effect on body weight. Average age, when

provided, was 49 and 51 years old for adults, and in one trial of children was 9.6 years old. Patients were 19–87% female. When stated, patients were overweight or obese. Trials were excluded if they enrolled patients with chronic diseases associated with obesity, patients on any therapy which influenced body weight, those having bariatric surgery, or treated for sleep apnea. Interventions included small-group cognitive behavioral therapy to improve sleep duration, increased or decreased time in bed (by about 1.5 hours per week), an education curriculum to improve sleep, diet and exercise, or breathing training on the didgeridoo to improve daytime sleepiness. The interventions ranged in duration from 2 to 16 weeks. There was a modest reduction in body weight associated with increased sleep duration (4 studies, n=117; standardized mean difference –0.54; 95% CI, –1.01 to –0.07; I^2=35%). Limitations of the analysis included the short duration of interventions (only 2 of the trials lasted at least 4 weeks) and the small number of studies available for comparison, as well as risk of bias due to lack of blinding personnel in two of the four studies.

A 2020 cohort study evaluated the association between sleep duration and weight loss in 1,202 patients from a prior RCT who already achieved clinically significant weight loss.[2] Patients, 69% women, were adults who lost greater than or equal to 5% of their body weight in the previous 12 months and who had a body mass index (BMI) of at least 25 kg/m^2 prior to their weight loss. Patients' average age was 45 years old and average BMI 30 kg/m^2. Patients lost on average 12 kg of body weight prior to entering the study. Only 8.5% of the cohort were current smokers and 53% were never smokers. Patients who were pregnant or breastfeeding, previously diagnosed with an eating disorder, unable to exercise, or who were new-onset type 1 diabetics were excluded. Sleep duration was measured using a wearable FitBit® device. Patients were grouped into sleep duration categories: <6 hours, 6 to <7 hours, 7 to < 8 hours, 8 to <9 hours, and ≥9 hours averaged over 14 nights of sleep. Patients with less than eight days of sleep data were excluded. When adjusted for covariates, patients with the shortest sleep duration (<6 hours) had significantly higher BMI compared to the other sleep durations (34 kg/m^2 vs 29 to 31 kg/m^2; P<.001). BMIs were similar between sleep durations 6 to <7, 7 to <8, 8 to <9, and ≥9 hours duration (31, 30, 29, and 30 kg/m^2; values extrapolated from a figure). There were no reported harms. The study was limited by inability to blind participants to their sleep being measured and researchers did not have access to patients' sleep duration prior to their enrollment in the study. EBP

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Does outpatient management of acute pulmonary embolus have similar outcomes as inpatient management?

EVIDENCE-BASED ANSWER

Yes. There is no difference in mortality, major bleeding, or reoccurrence with outpatient versus inpatient management of acute pulmonary embolus in low-risk patients (SOR: **B,** meta-analyses of randomized controlled trials (RCTs) and prospective cohort studies of limited quality and size).

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A 2019 systematic review and meta-analysis of two RCTs (N=453) compared the efficacy and safety of outpatient versus inpatient management of pulmonary embolus (PE).[1] Included studies were limited to RCTs that evaluated inpatient versus outpatient treatment of low-risk patients 18 years or older with an acute PE. Low-risk stratification was based on

either the pulmonary embolism severity index (risk classes I or II) or in accordance with the Hestia Criteria for outpatient PE treatment, both validated methods. Outpatient management was defined by hospitalization lasting <24 hours. In one study, all patients were treated with low-molecular-weight heparin (LMWH) and vitamin K antagonist (VKA). In the other study, outpatients were treated with rivaroxaban, whereas inpatients received local standard of care (typically bridging therapy with heparin and then VKA or direct oral anticoagulant). Outcomes included all-cause mortality, reoccurrence of PE at 90 days, and major bleeding (fatal or clinically symptomatic bleeding into a critical area, bleeding leading to fall in hemoglobin≥2 g/L, or transfusion≥2 units). Pooled analysis did not demonstrate any significant difference between outpatient versus inpatient groups for 30-day mortality (relative risk [RR], 0.33; 95% CI, 0.01–8.0), 90-day mortality (RR, 0.98; 95% CI, 0.06–16), major bleeding at 14 days (RR, 4.9; 95% CI, 0.24–102), major bleeding at 90 days (RR, 6.9; 95% CI, 0.36–132), or recurrent PE at 90 days (RR, 3.0; 95% CI, 0.12–72). The small number of included studies, patients, and reported events with wide confidence intervals raises the possibility of missing a small difference in outcomes. Additional studies with larger sample sizes are recommended.

A 2020 systematic review and meta-analysis identified three additional prospective cohort studies (N=234), in addition to the two RCTs included in the above review that evaluated the safety and efficacy of home versus hospital management of acute PE[2]. Inclusion criteria were RCTs or prospective cohort studies comparing outpatient versus inpatient treatment of adults 18 years or older with acute PE. Home management was defined as hospitalization lasting <72 hours. Low-risk classification in the cohort studies varied, with one using an unvalidated prediction tool and the two others using the absence of a variety of risk factors such as hemodynamic instability, high-risk comorbid conditions, hypoxia, increased bleeding risk, or contraindications to LMWH. All patients in the cohort studies were treated with LMWH with VKA or LMWH alone. Outcomes included all-cause mortality and major bleeding (same definition as above). Pooled data from the prospective cohort studies did not reveal any significant difference in 30 day all-cause mortality (RR, 0.81; 95% CI, 0.42–1.6), 90 day all-cause mortality (RR, 0.81; 95% CI, 0.42–1.6), or major bleeding at 90 days (RR, 2.7; 95% CI, 0.11–63). Limitations of the cohort studies include variability in low-risk stratification and high risk of bias because of the lack of adequate adjustment for possible confounders, objective assessment of outcomes, and loss of follow-up information. EBP

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Do cognitive activities reduce the risk of developing mild cognitive impairment or dementia?

EVIDENCE-BASED ANSWER

Participation in cognitive leisure activities is associated with reduced risk of developing amnestic mild cognitive impairment (aMCI) or dementia (SOR: **B**, based on systematic review of longitudinal cohort studies and case-control studies). Multiple professional organizations state that clinicians may offer cognitive interventions to reduce risk of dementia and MCI in adults with normal cognition (SOR: **C**, based on expert opinion and panel consensus).

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A 2016 systemic review and meta-analysis (19 studies; N=32,546) examined the relationship between

TABLE 1. Risk of dementia with cognitive leisure activities[1]

No. of studies	N	Cognitive leisure activities	Outcome (95% CI)
2	11,204	Crosswords, playing cards, and computer use	Hazard ratio 0.58 (0.46–0.74)
3	1,932	Reading books/newspapers, writing, and studying	Relative risk 0.61 (0.42–0.90)
2	1,276	Novelty activities and intellectual activities of reading, jigsaw/crossword puzzles and playing music	Odds ratio 0.78 (0.67–0.90)

cognitive leisure activities and the risk of developing cognitive impairment and dementia.[1] Of the 19 articles, 17 were longitudinal cohort studies with matched controls and two were case-control studies. Patients were healthy adults who were surveyed or interviewed regarding participation in unstructured cognitive leisure activities. Examples of cognitive leisure activities included crosswords and jigsaw puzzles, reading books or newspapers, playing music, and participation in hobbies (eg, gardening, knitting). The mean age was 77 years old, and no patients had a prior diagnosis of cognitive impairment or dementia. Studies with structured interventions (eg, formal course or professionally delivered programs) and that did not monitor participants based on standardized criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition were excluded. Studies were grouped by outcome (cognitive decline; cognitive impairment including aMCI, MCI, and dementia) along with the type of output (risk, odds, or hazards ratios), which led to five separate meta-analyses. The mean study follow-up was 7.2 years (range, 1–22.8 years). Three meta-analyses demonstrated reduced risk for dementia with participation in cognitive leisure activities (see **TABLE 1**). Two meta-analyses were performed focusing on the outcome for the risk of cognitive decline and impairment. One of the two meta-analyses demonstrated odds reduction with participation in cognitive activities (see **TABLE 2**). Overall, four of five meta-analyses demonstrated an association between participation in cognitive activities and reduced risk of cognitive impairment and dementia. A key limitation of the systematic review was lack of standardized classification of cognitive leisure activities among the studies. Also, some of the studies included participants with risk factors associated with cognitive impairment and dementia such as apolipoprotein E genotype, vascular health, tobacco use, and socioeconomic status.

TABLE 2. Risk of cognitive decline and impairment with cognitive leisure activities[1]

No. of studies	N	Cognitive leisure activities	Outcome (95% CI)
5	5,261	Reading, use of a computer, and hobbies (eg, gardening, traveling, and knitting)	Odds ratio 0.69 (0.56–0.85)
3	6,310	Reading, writing, crosswords, and board games	Hazard ratio 0.85 (0.71–1.02)[a]

[a] Nonsignificant.

A 2019 guideline from the World Health Organization stated "cognitive training may be offered to older adults with normal cognition and with MCI to reduce the risk of cognitive decline and/or dementia."[2] This recommendation was based on low quality of evidence from one systematic review that conducted a meta-analysis.

A 2017 clinical practice guideline from the American Academy of Neurology determined that insufficient evidence existed to support or refute cognitive interventions, although clinicians could recommend them.[3] EBP

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In patients with subclinical hypothyroidism, does treatment with levothyroxine improve quality of life?

EVIDENCE-BASED ANSWER

In nonpregnant adults with subclinical hypothyroidism, levothyroxine supplementation does not improve quality of life or thyroid-related quality of life symptoms in comparison to placebo. (SOR: **A**, meta-analysis of high quality randomized controlled trials). A collaboration between the British Medical Journal and the "Making GRADE the Irresistible Choice" Evidence Ecosystem Foundation similarly advises against thyroid supplementation in patients with subclinical hypothyroidism (SOR: **C**, consensus guideline).

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A 2018 systematic review and meta-analysis evaluated the effect of thyroxine/levothyroxine supplementation versus placebo or no supplementation on general and thyroid-related quality of life in nonpregnant adults with subclinical hypothyroidism.[1] Subclinical hypothyroidism was defined by the presence of an elevated serum thyroid-stimulating hormone (TSH) concentration in association with normal values of serum-free thyroxine. Studies were included if they maintained thyroid hormone therapy for at least one month, had a minimum follow-up of three months (range 3–18 months), and the control group received either placebo or no thyroxine/levothyroxine supplementation. Studies were excluded if they included pregnant adults, used pseudorandomization, or if subclinical hypothyroidism was not the primary focus of the study. Twenty-one randomized control trials (N=2,192) of adults 32 to 74 years old met the inclusion criteria. Four studies (n=796) reported general quality of life using three different instruments: the General Health Questionnaire; the Short Form 36; and the five dimension EruoQol instrument. Four studies (n=858) evaluated thyroid-related quality of life/hypothyroid symptoms using four different instruments: the Billewicz score; the 18-Item Underactive Thyroid-Dependent Quality of Life scale; the Zulewski score; and the thyroid-related quality of life patient-reported outcome measure. Pooled outcomes were reported as standardized mean differences (SMD) for general quality of life and thyroid-related quality of life/hypothyroid outcomes. Positive SMDs favored thyroid hormone supplementation and values of 0.2, 0.5, and 0.8 roughly translated to small, moderate, and large magnitudes of effect. Although thyroid hormone supplementation for the treatment of subclinical hypothyroidism lowered the average TSH toward the reference range compared with placebo (TSH range, 0.5–3.7 mIU/L vs 4.6–15 mIU/L), it did not improve the general quality of life (SMD, –0.1; 95% CI, –0.3 to 0.0) or thyroid-related quality of life/hypothyroid symptoms (SMD, 0.0; 95% CI, –0.1 to 0.1) in comparison to placebo or no thyroxine/levothyroxine supplementation.

A 2019 clinical practice guideline based on the meta-analysis above stated that there are no clinically relevant benefits to thyroid hormone replacement therapy for general quality of life or thyroid-related quality of life/hypothyroid symptoms in adults with subclinical hypothyroidism.[2] This guideline recommended that clinicians refrain from initiating thyroid hormone replacement therapy in adults with subclinical hypothyroidism and instead be surveillant for thyroid function decline. EBP

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What are the most effective office-based strategies to increase vaccine uptake among vaccine-hesitant parents?

EVIDENCE-BASED ANSWER

It's not clear. Overall, face-to-face interventions modestly increase vaccine uptake in children but do not change parental attitudes toward vaccination (SOR: **A**, systematic review of randomized controlled trials [RCTs]). Personalized and interactive programs are no more effective than standard education programs (SOR: **B**, two RCTs). Educational videos and handouts may decrease vaccine hesitancy but do not increase vaccine uptake (SOR: **B**, single RCT).

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A 2018 systematic review of seven RCTs and three cluster RCTs (N=4,527) assessed the impact of face-to-face interventions on parental decisions to vaccinate children from infancy to six years old.[1] Face-to-face interventions included group discussions, structured home visits, and one-on-one educational sessions. Among the included trials, interventions were single or multiple sessions, lasting a couple minutes to a couple hours, occurring during the third trimester of pregnancy and up to six months postpartum. Because of heterogeneity among scoring systems in different trials, some outcomes were pooled and systematized into a standardized mean difference (SMD). When compared with no education or impersonal education, face-to-face interventions significantly increased vaccine uptake in children (7 trials, n=3,004; risk ratio, 1.2; 95% CI, 1.04–1.4), while producing only a small increase in parental knowledge (4 trials, n=657; SMD, 0.19; 95% CI, 0.001–0.38). However, no significant change was found in parental beliefs regarding disease severity or need for vaccines regardless of whether parents received face-to-face intervention or other education.

A 2016 RCT (N=888) examined if web-based interventions with interactive social media content were more effective in reducing vaccine hesitancy than webpages with noninteractive content.[2] Patients were pregnant women in the third trimester with no history of fetal demise, miscarriage, or congenital abnormality. They were randomized to receive interactive social media content (n=542), noninteractive web-based media content (n=371), or standard care (n=180). The babies from these pregnancies were then followed from birth to 200 days to determine which group had the highest proportion of fully vaccinated children. When compared with the usual care group, the vaccination rate was significantly higher in the interactive program group (odds ratio [OR], 1.9; 95% CI, 1.1–3.5). However, the vaccination rate of the interactive program was not significantly better than the noninteractive webpage group (OR, 1.2; 95% CI, 0.70–2.0).

A 2013 blinded RCT (N=77) investigated the impact of personalized educational material on reducing hesitancy for the measles, mumps, and rubella vaccine (MMR).[3] Parents of children younger than six years at primary care offices within a single organization were screened for hesitancy based on stating that they "did not want" or were "unsure" about the MMR vaccine. Both the control group (n=41) and the intervention group (n=36) received access to educational content derived from the Centers for Disease Control and Prevention's MMR Vaccine Information Statement, but only the intervention group received personalized content via a computer algorithm to address any stated concerns of the parent. Overall, both groups experienced a significant increase in their intent to vaccinate against MMR compared with base-

line (52% vs 34%; $P=.01$), but no significant difference was found between the personalized and nonpersonalized groups in intent to vaccinate (58% vs 46% $P=.48$).

A 2013 cluster RCT (N=122) measured whether a combination of educational resources was effective in reducing vaccine hesitancy and improving vaccine uptake.[4] Parents of infants at their two-week well-child visit were recruited from private pediatric offices and screened for vaccine hesitancy using the Parent Attitudes about Childhood Vaccines (PACV) survey, a 100-point scale with higher numbers indicating greater hesitancy. Parents scoring 25 or higher were identified as vaccine hesitant and invited to enroll in the trial. The intervention group (n=55) received access to three educational materials: an eight-minute video, a handout on common vaccine concerns, and instructions on how to find accurate medical information on the Internet. The control group (n=67) received routine care. At the two-month well-child visit, parents took the PACV survey again. The intervention group was significantly less vaccine hesitant after two months compared with baseline per the PACV (33 vs 40 points; $P=.049$). Ultimately, no significant difference was observed in the intervention group compared with the control group in two-month vaccinations at 12 weeks (83% vs 82%; $P=.86$). EBP

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Is parental weight loss during a family-oriented, pediatric weight loss program correlated with pediatric weight change in that program?

EVIDENCE-BASED ANSWER

Parental weight loss as assessed by body mass index positively correlated with pediatric weight loss during pediatric obesity programs (SOR: **B**, small randomized controlled trials [RCTs] and a secondary analysis of small RCTs).

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A 2014 RCT (N=96) analyzed the parental-child weight loss relationship in a childhood weight management program.[1] Participants were overweight children in the 85th percentile of body mass index (BMI) aged 2 to 5 years old with an overweight parent (BMI greater than 25 kg/m^2). Children were excluded if too small for gestational age, possessed a short stature, or could not be active. Researchers randomized children to either a parent-child behavioral intervention and educational program group (n=46) or a child-only educational program group (n=50). Thirteen 60-minute sessions were delivered over one year with 10 intersession phone calls. Three follow-up sessions occurred over the subsequent year. The primary outcome was the correlation between parental BMI change and child percent over BMI change using Pearson correlation coefficients. Parent weight (BMI) and child weight (percent over BMI) significantly correlated from baseline to 12 months (r=0.38; $P<.001$), 18 months (r=0.35; $P=.004$), and 24

months (r=0.26; $P<.03$) for both groups. Decreases in standardized BMI (z-BMI) were greater for the children in the intervention versus control group, respectively, with z-BMI at six months (1.7 vs 1.9; $P<.001$), 12 months (1.7 vs 1.9; $P<.001$), 18 months (1.7 vs 1.9; $P<.01$), and 24 months (1.6 vs 1.9; $P<.007$), compared with baseline.

A 2012 RCT (N=80) examined the influence of parent BMI on child BMI in a childhood obesity program.[2] Patients were overweight children (mean BMI 29 kg/m^2) with a mean age of 11 years and their parents (89% female, mean BMI 32 kg/m^2). Children were excluded if already enrolled in a weight management program, had a medical condition affecting participation, or used a medication affecting appetite. Children and parents were randomized to either parent-only education groups (n=40) or parent and child groups (n=40). The education program delivered weekly 60-minute educational sessions on nutrition, physical activity, behavioral change, and parenting skills in groups of 6 to 10 participants groups over a five-month period. A mixed model analysis was used to predict child BMI at baseline, posttreatment, and follow-up at 11 months. Results were adjusted for parenting skills, home food environment, income, and demographic data. In both parent-only and parent-and-child groups, a one unit decrease in parental BMI significantly correlated with a 0.26 decrease in child BMI after controlling for all other variables posttreatment and in follow-up at 11 months (ß=0.26; 95% CI, 0.10—0.41). No significant difference was observed between the parent-only group and the parent-child group in overall weight loss. Limitations included lack of blinding, small sample size, and greater proportion of participating mothers than fathers.

A 2004 secondary analysis of three RCTs (N=142) examined whether changes in parental BMI independently predicted changes in child BMI in identical family-based weight control programs.[3] Participants included children aged 8 to 12 years in the 85th percentile BMI or greater with a parent in the 70th percentile or greater. Education was provided on nutrition based on the Traffic-Light diet and a physical activity program, in addition to environmental changes to support behavior change. Each study observed participants during a two-year period with assessments at baseline and six, 12, and 24 months. In trial one (n=52), children were assigned to one of four groups that varied the targeted behaviors (sedentary behaviors vs physical activity) and treatment dose (low vs high). In trial two (n=45), children were assigned to one of three groups that were enrolled in a six-month family-based behavioral weight control program plus parent and child problem solving, child problem solving, or standard treatment with no additional problem solving. In trial three (n=45), children were assigned to groups that differed in how they reduced targeted sedentary behaviors, comparing a reinforcement system versus restructuring of the environment. Hierarchical regression models were used to determine the influence of change in parent BMI on child BMI from 0 to 6 months and 0 to 24 months while accounting for differences in child and parent sex, socioeconomic status, age, and baseline BMI. A 1-unit decrease in parent BMI was associated with a 0.46 decrease in child BMI from 0 to 6 months (ß=0.46; 95% CI, 0.31—0.61) and a 0.29 decrease in child BMI from 0 to 24 months (ß=0.29; 95% CI, 0.07—0.51). EBP

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In elderly patients with advanced dementia, does donepezil improve overall function?

EVIDENCE-BASED ANSWER

For patients with mild to severe Alzheimer disease, donepezil 10 mg is associated with mildly improved clinician-rated global impression scales (CRGICSs), cognitive function, and activities of daily living compared with placebo. No difference was observed compared with placebo for behavioral symptoms or quality of life (SOR: **A**, systematic review).

Donepezil 10 mg but not 5 mg improves cognitive function compared with placebo in patients with Lewy body dementia, but neither dose significantly improves behavioral symptoms (SOR: **B**, randomized placebo-controlled trial).

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A 2018 systemic review of 30 randomized controlled trials (RCTs; N=8,297) looked at the efficacy and safety of donepezil in patients with mild, moderate, and severe Alzheimer dementia.[1] Patients were men and women, 39 to 94 years old. Included patients had Alzheimer dementia (typically based on National Institute of Neurological and Communicative Disorders and Stroke and Communication Disorders and the Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA], Diagnostic and Statistical Manual of Mental Disorders [DSM] III, or DSM IV Criteria), and a baseline mini-mental status examination (MMSE) score of <27. The NINCDS-ADRDA is a set of criteria used to diagnose Alzheimer dementia based on clinical findings. Treatment group donepezil doses were generally 5 to 10 mg, with two studies using 23 mg. Study durations were typically 24 weeks but ranged from 12 to 60 weeks. Primary outcomes were safety and efficacy of donepezil 10 mg compared with placebo after 26 weeks of treatment. The CRGICS is a seven-point scale looking at improvement in a patient's illness over time; patients taking donepezil 10 mg compared with placebo were more likely to have improved CRGICS scores (6 studies, N=1,674, odds ratio [OR], 1.92; 95% CI, 1.54–2.39). Treatment was also associated with better cognitive function outcomes as measured with the MMSE (range, 0–30, lower scores indicating greater impairment; 3 studies, N=1,348, mean difference [MD], 1.05; 95% CI, 0.73–1.37). Donepezil was also associated with improved performance on the Alzheimer's disease assessment scale-cognitive (ADAS-Cog) (range, 0–70, higher scores indicating greater impairment; 5 studies, N=1,130, MD, –2.67; 95% CI, –3.31 to –2.02) and on the severe impairment battery (range, 0–100, lower scores indicating greater impairment; 5 studies, N=1,348, MD, 5.92; 95% CI, 4.53–7.31). Compared with placebo, donepezil was associated with better function measured with the Alzheimer's Disease Cooperative Study Activities of Daily Living for severe Alzheimer disease (range, 1–54, higher scores indicating greater improvement; 3 studies, N=733, MD, 1.03; 95% CI, 0.21–1.85). For behavioral symptoms, no difference was observed between placebo and donepezil, as measured by the neuropsychiatric inventory (NPI) or the behavioral pathology in Alzheimer's disease scale.

Donepezil 10 mg versus 5 mg showed a significant benefit in cognitive function, as measured by the ADAS-Cog (MD, –1.05; 95% CI, –1.8 to –0.3). No difference was observed between these doses for quality of life, global assessment, or behavioral changes. No greater benefits of 23 mg/d versus 10 mg/d donepezil were observed, but adverse events and study withdrawal rates were higher. Patients taking donepezil were more likely to experience adverse effects (including anorexia, nausea, vomiting, and diarrhea) compared with patients taking placebo (10 studies, N=2,500, 72% vs 65%; OR, 1.59; 95%, CI 1.31–1.95). There were decreased adverse events in 5 mg versus 10 mg groups, and the patients in the 5 mg group were less likely to dropout of the study because of adverse events (3 studies, 1,052 participants; OR, 2.41; 95% CI, 1.63–3.57). No difference was noted in deaths between 5 mg donepezil, 10 mg donepezil, and placebo groups.

A 2015 RCT not included in the above meta-analysis (N=142) compared donepezil with placebo in participants with dementia with Lewy bodies.[2] Included patients were 50 years old or older with mild to moderate or severe

dementia, defined as MMSE 10 to 26, as well as presence of psychiatric symptoms defined by NPI-2 of ≥1, and the NPI Plus (NPI-Plus) of ≥8. The NPI-2 is administered by caregivers and measures behavioral disturbances in dementia patients. It includes 10 domains: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor activity. The NPI-Plus includes the same 10 domains and also includes sleep and cognitive fluctuation. Participants were randomized to receive placebo, 5 mg donepezil daily, or 10 mg donepezil daily for 12 weeks. Primary outcomes were cognitive improvement, using the clinician administered MMSE, and behavioral and neuropsychiatric symptoms measured by the NPI-2. MMSE scores significantly improved compared with placebo group for participants taking 10 mg of donepezil daily (2.2 vs 0.6 point improvements; $P=.016$). MMSE scores did not significantly improve in patients taking 5 mg versus placebo (–1.4 vs –0.6 point improvements; $P=.232$). No differences were found in NPI-2 scores compared with placebo in participants taking 10 mg and 5 mg of donepezil daily (–2.9 vs –2.0 point improvements; $P=.391$; –1.7 vs –2.0 point improvements; $P=.661$, respectively). Adverse events (including nausea, decreased appetite, pyrexia, and nasopharyngitis) did not significantly differ substantially among the placebo, 5 mg, or 10 mg groups. The incidence of adverse events that led to discontinuation of donepezil was higher in the 5 mg group compared with placebo (21.3% vs 10.9%) but was lower in the 10 mg group compared with placebo (4.1% vs 10.9%). EBP

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Does treatment of iron deficiency anemia in asymptomatic pregnant women improve maternal pregnancy outcomes?

EVIDENCE-BASED ANSWER

In asymptomatic pregnant women with iron deficiency anemia, iron supplementation may reduce the risk of anemia at term by about 70%, but if it improves clinical pregnancy outcomes remains unclear (SOR: **B**, systematic review of randomized controlled trials with inconsistent results). Nevertheless, all iron deficient pregnant women should receive iron therapy (SOR: **C**, expert opinion).

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A 2015 systematic review of 12 randomized controlled trials (RCTs; N=3,841) from Australia, Europe, Hong Kong, Iran, and the United States evaluated the impact of routine screening and treatment of iron deficiency anemia (IDA) on maternal and fetal health outcomes in asymptomatic pregnant women.[1] The mean age of patients in the studies ranged from 24 to 31 years old. The number of patients in each study varied from about 40 to 1,100. Treatment of IDA was evaluated by comparing an intervention group that received iron supplementation with a control group that received placebo. Seven studies initiated iron supplementation before 20 weeks' gestation, whereas five studies initiated iron supplementation at 20 weeks' gestation. Most studies concluded treatment at birth. The daily dose of elemental iron ranged from 20 to 200 mg administered in various formulations: seven studies used ferrous sulfate, one used ferrous fumarate, and four used an unspecified form of elemental iron. Maternal outcomes varied among studies and included IDA, iron deficiency and anemia rates; maternal hematologic indices; and maternal quality of life.

Outcomes were measured at various time points and included third trimester, delivery, and in the postpartum period. Pooled analysis of four trials (N=762) indicated that iron supplementation compared with placebo treatment reduced the risk of maternal IDA at term (relative risk 0.29; 95% CI, 0.17–0.49). One RCT (N=430) evaluated maternal quality of life during or after pregnancy and found no differences between women receiving iron supplementation versus placebo. The effect of iron supplementation on cesarean delivery rates was inconclusive. One large trial (N=1,164) found that supplementation with 60 mg of elemental iron, when compared with placebo treatment, was associated with a lower cesarean delivery rate (25.2% vs 33.1%, respectively; odds ratio 0.58; 95% CI, 0.37–0.89); however, no significant effect of iron supplementation was noted on cesarean delivery rates in four smaller trials ranging in size from 97 to 727 women. The review was limited by small sample size in some studies, and significant heterogeneity in methodology, iron formulation and dose, and outcomes reported.

A 2008 evidence-based clinical practice guideline on anemia in pregnancy from the American College of Obstetricians and Gynecologists (ACOG) concluded that iron supplementation reduces anemia prevalence at delivery (level A recommendation, based on good and consistent scientific evidence).[2] The ACOG guideline recommended that iron supplements and prenatal vitamins be given to all pregnant women with iron deficiency anemia (level C recommendation, based on consensus and expert opinion). EBP

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Is acupuncture effective in treating anxiety?

EVIDENCE-BASED ANSWER

Auricular acupuncture and body acupuncture may be moderately effective in reducing both state and trait anxiety (SOR: C, low-quality randomized controlled trial and prospective cohort study). Anxiety reduction with auricular acupuncture appears comparable with progressive muscle relaxation (SOR: C, nonblinded prospective parallel trial).

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A 2015 randomized control trial (N=40) evaluated the effectiveness of acupuncture in the treatment of adults with chronic anxiety that was not well controlled after routine interventions (advice, medications, bibliotherapy, and Cognitive Behavioral Therapy).[1] Participants were randomized to receive 10 weeks of standardized body acupuncture treatments using points pericardium (PC6), heart (HT7), and liver (LR3) bilaterally (n=25, mean age 42), or waiting until after 10 weeks to receive the same 10-week body acupuncture treatment (n=15; mean age, 45 years). Both groups were followed for 10 weeks after receiving acupuncture. The groups were evaluated using the State and Trait Anxiety Index (STAI), which measures both state and trait anxiety separately. State anxiety reflects the temporary psychologic and physiologic response to a situation, whereas trait anxiety is a consistent pattern of behavior and the tendency to present with state anxiety during a situation. Scores ranged from 20 to 80, with higher scores indicating greater anxiety. After the initial 10 weeks, treatment group mean state anxiety scores decreased 19 points (95% CI, –15 to –22) compared with a 0.8-point decrease (95% CI, –3.2 to 4.8) in the waiting list group ($P<.0001$). Mean trait anxiety scores decreased by 22 points (95% CI, 16–28) in the treatment group compared with a reduction of 1.2 points (95% CI, –2.6 to 0.16) in the waiting list group ($P<.0001$). A similar reduction was seen for both mean state and trait anxiety, respectively (mean score

TABLE. Change intensity index scores for patients with anxiety treated with auricular acupuncture or progressive muscle relaxation compared with baseline[3]

	Auricular acupuncture group		Progressive muscle relaxation group	
	Mean	P	Mean	P
Week 1 (n=136)	68	.000	77	.000
Week 2 (n=104)	81	.000	92	.118
Week 3 (n=82)	85	.004	85	.002
Week 4 (n=76)	90	.017	95	.393

reduction: 22; 95% CI, –17 to –27; and –21; 95% CI, –16 to –26) in the waiting list group after receiving the acupuncture treatment. Benefits were maintained in both groups at the 10-week follow-up, with no adverse effects reported. Limitations include small sample size and lack of blinding.

A 2018 prospective cohort study (N=112) evaluated the effectiveness of auricular acupuncture in decreasing anxiety in health care workers.[2] Adult participants were from the cardiovascular unit in one hospital and had recently experienced an on-site violent incident that resulted in a colleague's death. Participants underwent five sessions of auricular acupuncture using the National Acupuncture Detoxification Association (NADA) protocol over a 16-week period. Of the 112 participants, only 83 completed the first session, and 42 (2 men and 40 women) participants completed all five sessions. Each session consisted of auricular acupuncture with needles left in place for 30 minutes. Before and after each session, participants were evaluated with STAI. Mean STAI state anxiety scores decreased from 38 to 33 (P=.0001) between pre- and post- intervention. Mean STAI trait anxiety scores decreased from 38 to 35 (P=.0001) for pre- and postintervention. Limitations include small sample size from one unit within a single hospital, high dropout rate, and lack of control group.

A 2016 prospective parallel group clinical trial (N=162) compared the effects of auricular acupuncture and progressive muscle relaxation (PMR) in the treatment of anxiety disorder or major depression disorder.[3] Participants with anxiety disorder (n=96) based on Diagnostic and Statistical Manual of Mental Disorders IV criteria chose between either treatment with auricular acupuncture (n=53) or progressive muscle relaxation (n=43). All participants also received personal and group cognitive behavior therapy and psychopharmacologic treatments. Preceding and immediately after treatment, participants rated their anxiety level using the visual analog scale (VAS, scale 0–100). Auricular acupuncture treatment followed the standardized NADA protocol bilaterally, and progressive muscle relaxation followed the Berstein and Borkovec method, with each treatment provided twice a week for four weeks. Because of incomplete data from high dropout rates (35%), a change intensity (CI) index was used for statistical evaluation. Equal pre- and post-VAS scores would give a CI score of 100. The further the CI score is away from 100, the larger the difference in pre- and post-VAS scores. Both auricular acupuncture and progressive muscle relaxation were effective in decreasing anxiety levels (see **TABLE**). Limitations include high dropout rates and nonrandomized study design. EBP

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Do scribes improve patient satisfaction in the primary care setting?

EVIDENCE-BASED ANSWER

It does not appear so. Scribes do not improve patient satisfaction in primary care (SOR: **B**, single randomized controlled trial [RCT] and cohort). However, scribes do improve physician satisfaction and charting time (SOR: **B**, single RCT and cohort).

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A 2016 randomized controlled trial (with 4 physicians, 2 scribes, and 1,475 patient encounters) examined the effect of medical scribes in an academic family medicine clinic.[1] Four physicians and two scribes at the clinic were randomized to one week with a scribe then one week without a scribe over the course of one year. Outcomes measured included physician satisfaction, physician chart quality and accuracy, and patient satisfaction. A six-item questionnaire explored patients' perception of provider communication, listening skills, engagement, compassion, and time spent (measured by completion of chart before or after 48 hours). Both questionnaires for physicians and patients used a 7-point Likert scale, with one indicating strong disagreement and seven indicating strong agreement. For data analyses, each answer was dichotomized into strongly satisfied versus nonstrongly satisfied (7 vs 1 to 6). Scribes produced significantly higher physician satisfaction scores over 361 total sessions in all aspects of care and charting compared with no scribe used (odds ratio [OR] 10.8; 95% CI, 5.4–22), but scribes had no significant effect on patient satisfaction compared with sessions without a scribe (OR 1.1; 95% CI, 0.60–1.9). Scribes did significantly improve charting completion under 48 hours compared with no scribes (OR 1.2; 95% CI, 1.02–1.4). No harms of implementing scribes were noted. A key limitation was that few physicians and scribes participated in the study.

A 2017 prospective, pre-post pilot study (N=325) evaluated the impact of using scribes on physician workplace and patient satisfaction.[2] Six General Internal Medicine faculty, one full-time scribe, and a sample of 325 of their patients were included. The scribe worked with each faculty a minimum of one clinic session a week and the remainder of the time was available for each faculty. A 27-item postvisit survey assessed patient's satisfaction during visits with a scribe (n=166) and without (n=159) a scribe. Outcomes measured were physician workplace satisfaction and burnout, time spent on electronic medical record documentation, patient satisfaction with doctor-patient relationship, and patient's overall attitude toward scribes. A 21-item prequestionnaire and 44-item postquestionnaire was used to assess physician satisfaction. Patient attitude and satisfaction levels were measured via a 27-item questionnaire with Likert scales. When compared with no scribe present, the addition of a scribe did not significantly improve patient understanding rate (85% vs 87%, $P>.05$) or the rate of patients who felt the physician "spent enough time" with them (85% vs 85%, $P>.05$). Scribes did significantly improve times spent on documentation compared with no scribes per session (0.76 vs 1.7 hours, $P=.02$). Limitations of the study included a small physician sample size and short duration of the pilot study, which limited the ability to detect a change in patient satisfaction. EBP

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What is the appropriate treatment of measles in immunocompetent pediatric patients?

EVIDENCE-BASED ANSWER

High-dose vitamin A supplementation (50,000–200,000 IU, dosed by age) given twice over two days reduces the risk of all-cause mortality in children under two years old with measles (number needed to treat [NNT]=15). A single dose of vitamin A is not effective (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Experts recommend that clinicians give vitamin A once daily for two days to all children with acute measles, especially if severe, at the above age-specific doses, and repeated in 2 to 4 weeks for children with vitamin A deficiency (SOR: **C**, consensus guideline).

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A 2005 meta-analysis on the effects of vitamin A for the treatment of measles in children included eight controlled trials (N=2,574); seven of these (N=1,974) were randomized and five (N=1,500) were double-blinded.[1] The patients were 15 years old or younger. The studies took place in Africa, Japan, and England, and measles-related mortality rates varied from 0% to 14.9% (average 8.9%). They included hospitalized (N=1,428) and community dwelling (N=1,146) patients. One trial (N=600) was published in 1932 and the remaining seven were published between 1987 and 1999. The interventions were oral vitamin A, either water-based or oil-based, dosed between 50,000 and 200,000 IU, and administered either as a one-time dose or daily over two days. Control group patients received placebo or usual care without vitamin A. Pooled outcomes for the randomized controlled trials showed no reduction in mortality comparing vitamin A with placebo (7 trials, N=1,974; relative risk [RR] 0.83; 95% CI, 0.51–1.3). However, in a subgroup analysis of the studies that gave two doses, a 6.6% absolute reduction was noted in mortality with vitamin A (3 trials, N=429; RR 0.4; 95% CI, 0.19–0.87; NNT=15). Vitamin A was more effective than placebo in preventing death in children younger than two years old (3 trials, N=309; RR 0.21; 95% CI, 0.07–0.66; NNT=11) but not in those older than two years old (2 trials, N=120; RR 0.98; 95% CI, 0.33–2.9).

A 2018 consensus-based guideline from the American Academy of Pediatrics (AAP) recommended clinicians give vitamin A to all children with acute measles (especially if severe) at age-specific doses of 50,000 IU for infants younger than six months old, 100,000 IU for infants 6 to 11 months old, and 200,000 IU for children 12 months and older (no strength of recommendation provided).[2] The AAP guideline recommended that the vitamin A dose be administered once daily for two days, and repeated 2 to 4 weeks later for children with signs and symptoms of vitamin A deficiency. EBP

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Does procalcitonin improve the accuracy of the diagnosis of CAP in the emergency department?

EVIDENCE-BASED ANSWER

Using a cutoff of 0.10 ng/mL for procalcitonin significantly helps improve the accuracy of a community acquired pneumonia diagnosis when combined with clinical symptom criteria such as dyspnea, fever, cough, and sputum production (SOR: **B**, secondary analyses of various clinical trials). However, in patients evaluated with a thoracic computed tomography, it is less predictive than a high-sensitivity C-reactive protein (SOR: **C**, post-hoc analysis without blinding).

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A 2016 secondary analysis combined two prospective cohort samples (N=453) to evaluate procalcitonin in the diagnosis of community acquired pneumonia (CAP) for patients who presented to an emergency department (ED) with acute dyspnea.[1] The weighted mean age was 65 years old and 52% were men. The gold standard used for diagnosis of CAP was an adjudication committee evaluating patients based on symptoms of cough, fever, sputum production, and pleuritic chest pain and a new infiltrate on a chest X-ray (CXR). The prevalence of CAP in the combined studies was 13%. Area under the curve (AUC) is a statistical test that can determine the accuracy of a diagnostic test. Generally, a score of 0.6 to 0.7 is poor, 0.7 to 0.8 would be fair, 0.8 to 0.9 would be good/moderate strong, and 0.9 to 1.0 would be strongly recommended. Procalcitonin level alone at greater than 0.10 ng/mL resulted in a sensitivity of 78%, specificity of 80%, and an AUC of 0.84 (95% CI, 0.77–0.91) for the diagnosis of CAP. Logistic regression models compared the diagnosis of CAP with and without procalcitonin. The addition of a procalcitonin cutoff level as a diagnostic criterion significantly improved the ruling in (improvement 25%, $P<.05$) and ruling out (improvement 29%, $P<.05$) of CAP compared with cases not using procalcitonin.

A 2007 secondary analysis of two randomized controlled trials (N=543) evaluated the diagnostic accuracy of adding procalcitonin to a clinical model for diagnosing CAP in patients presenting to a tertiary care ED with suspected-lower respiratory tract infections.[2] The gold standard for a diagnosis of CAP was an adjudication committee using clinical impression and CXR. A total of 373 patients (69%) were diagnosed with CAP, 63% were men, and the mean age was 67 years old. A clinical model including fever, cough, sputum production, abnormal chest auscultation, and dyspnea had an AUC of 0.79 (95% CI, 0.75–0.83). A procalcitonin cut-off of 0.1 ng/mL produced a sensitivity of 0.90 and a specificity of 0.59. The inclusion of procalcitonin significantly improved the diagnostic accuracy for CAP yielding an AUC of 0.88 (95% CI, 0.85–0.91). Combining samples from different studies may have introduced assessment bias. Additionally, prescribing antibiotics based on procalcitonin levels in the original studies may have introduced a bias in favor of procalcitonin.

A 2015 post-hoc analysis of a prospective interventional study (N=200) assessed the diagnostic accuracy of procalcitonin and high-sensitivity C-reactive protein (hsCRP) in adult patients presenting to EDs with clinically suspected CAP, who had a thoracic computed tomography (CT) scan done within four hours.[3] The mean age of included patients was 64 years old and 51% were men. The gold standard for diagnosis of CAP was an adjudication committee evaluation after 28 days based on the thoracic CT scan, clinical information, and follow-up data. Accordingly, 49% were diagnosed as definite CAP, 4% as probable CAP, 12% as possible CAP, and 36% as definitely not CAP. Diagnostic accuracy was evaluated by an AUC. AUC for hsCRP was 0.79 (95% CI, 0.72–0.86) with an optimal cut-off of 46 μg/mL and AUC for procalcitonin was 0.66 (95% CI, 0.57–0.74) with an optimal cut-off of 0.13 ng/mL. There was no significant difference between the two tests for diagnostic accuracy based on the AUC scores. The diagnosis of CAP and the operating characteristics of the biomarkers may have been biased because the adjudication committee was not blinded to the results of the biomarkers. EBP

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Is binge drinking in adults associated with increased mortality compared with moderate consumption of alcohol?

EVIDENCE-BASED ANSWER

Yes. Binge drinking and heavy drinking are associated with higher mortality rates compared with moderate drinking (SOR: **B**, consistent results from 2 high-quality cohorts). Physicians should screen for binge drinking in adults and provide quick behavioral counseling to help reduce unhealthy drinking habits (SOR: **B**, evidence-based guideline).

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A 2014 prospective cohort study (N=446) evaluated the effect of regular moderate drinking and episodic binge drinking on mortality.[1] Participants (75% male, 62 mean years old) were either self-reported moderate drinkers (n=372) or regular drinkers who also engaged in episodic binge drinking (n=72). Very light drinkers consuming less than one-half a standard alcoholic beverage per week were excluded from the study. Episodic heavy drinking was defined using the National Institute on Alcohol Abuse and Alcoholism definition of binge drinking—four drinks for women or five drinks for men at one time (about 2 hours) on at least one day in the past month, or any pattern of drinking resulting in a blood alcohol level of 0.08 g/dL. Regular moderate drinking was defined as up to one drink per day for women and two drinks per day for men. Final results were presented as an adjusted odds ratio (aOR) controlled for by age, gender, socioeconomic status, marital status, medical conditions, obesity, smoking, physical activity, depression, avoidance coping, number of close friends, and quality of friend support. At 20 years of follow-up, significantly more patients in the binge drinking group (n=45) died compared with patients in the regular moderate (n=137) drinking group (aOR 2.1; 95% CI, 1.1–4.0). A key limitation of the study was the reliance on self-reported drinking.

A 2017 retrospective cohort study (n=333,247) compared differing levels of alcohol consumption and mortality in nonpregnant adults with 8.2 median years of follow-up.[2] Alcohol intake was categorized into six groups that ranged from lifetime abstainers (less than 12 lifetime drinks) to current heavy drinkers (more than 7 drinks per week for women and more than 14 drinks per week for men). Patients were categorized as binge drinking if, in the past year, they had five or more alcoholic drinks on any day. The primary outcome was all-cause mortality and disease-specific mortality due to cancer, cardiovascular disease, heart disease, and cerebrovascular disease. Results were reported as hazard ratios (HRs) and controlled for by sex, age, race and ethnicity, education, lifestyle factors including body mass index, physical activity and smoking status, presence of hypertension, heart disease, stroke, cancer, and diabetes. Individuals who died within the first two years of the study were excluded. Each group was compared to lifetime abstainers as the control. Patients with binge drinking (152,322 person-years) had significantly increased all-cause mortality compared with lifetime abstainers (HR 1.2; 95% CI, 1.1–1.3). Non-binge drinkers had significantly lower all-cause mortality compared with lifetime abstainers (HR 0.81; 95% CI, 0.78–0.85). Compared with abstainers, cancer-specific mortality was significantly increased in binge drinkers (HR 1.3; 95% CI, 1.1–1.6) but not for non-binge drinkers. All other disease-specific mortality comparisons were similar between the two groups.

A 2018 evidence-based guideline statement from the United States Preventive Task Force recommended screening for unhealthy alcohol use for adults 18 years old and older, and providing brief behavioral counseling

to reduce unhealthy alcohol use in a primary care setting (grade B, moderate evidence).[3] EBP

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Does cell phone use increase the risk of cancer?

EVIDENCE-BASED ANSWER

Long-term (>10 years) cell phone use may be associated with an increased risk of glioma tumors (SOR: **B**, meta-analysis with moderate heterogeneity). Cell phone use may be associated with parotid gland tumors (SOR: **B**, meta-analysis with moderate heterogeneity).

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A 2018 meta-analysis (8 case-control studies, n=3,965; 2 cohort studies, n=690) evaluated the association between cell phone use and glioma risk.[1] Participants were greater than 16 years old from 13 different countries. Subgroup analyses were conducted for time since first use of cell phones, location of tumor, and laterality. Diagnostic criteria and severity of glioma were not specified in the analysis. Follow-up periods were not specified. Overall, adult gliomas were not associated with ever using cell phones (odds ratio [OR] 1.03; 95% CI, 0.92–1.16; I^2=54.2%). Subgroup analyses did not find an association between regular cell phone use (≥1 call a day for more than 6 months) and glioma (OR –0.81; 95% CI, –0.94 to –0.70) or temporal lobe location and cell phone use (n=3,238; OR 1.61; 95% CI, 0.78–3.33). A significant risk of gliomas was found in long-term users (use ≥10 years) (n=893; OR 1.33; 95% CI, 1.05–1.67). Limitations of this study included heterogeneity of studies, predominance of case-control studies, potential for recall and selection biases, and the potential for confounding changes in lifestyle after diagnosis.

A 2017 meta-analysis (3 retrospective case-control studies; n=5,087) evaluated the association between cell phone use and parotid gland tumors.[2] Patient ages ranged from 20 to 69 years old (mean age not provided). Gender information was unavailable for one study; in the two remaining studies (n=2,579), 52.4% of patients were female. The authors did not delineate study inclusion criteria nor descriptions of how cell phone use was determined. Tumors included both benign and malignant subtypes. The method of neoplasm identification was not described. Cell phone use was associated with higher rates of parotid gland tumors (OR=1.28; 95% CI, 1.09–1.51; I^2=51%). No subgroup analysis was included. This analysis was limited by a minimal description of inclusion criteria and unquantified cell phone use. EBP

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Is osteopathic manipulative treatment effective in reducing primary dysmenorrhea?

EVIDENCE-BASED ANSWER

Yes. Osteopathic manipulative treatment (OMT) effectively reduces pain intensity in women with primary dysmenorrhea (SOR: **C**, small randomized controlled trials [RCTs]). Additionally, OMT reduces menstrual pain duration (SOR: **C**, small RCT) and may physically improve the quality of life of those treated (SOR: **C**, small RCTs).

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A 2017 RCT (n=26) analyzed the efficacy of osteopathic manipulative treatment (OMT) in reducing menstrual pain and improving quality of life in Italian women with primary dysmenorrhea.[1] All patients had regular menstrual cycles, body mass index between 20 and 30 kg/m^2, and a "medical diagnosis" of primary dysmenorrhea. Exclusion criteria included pregnancy, secondary causes for dysmenorrhea, substance abuse, and participation in other clinical studies. The intervention group (n=13) received OMT every five days during two consecutive menstrual cycles, whereas the control group (n=13) received light touch therapy (LTT) on the same schedule. Light Touch therapy is a form of sham OMT that involves light-touch contact. One primary outcome measured was pain severity at the fifth and sixth menstrual cycles via a 0 to 10 numerical rating scale, with higher numbers representing increased pain, and quality of life by the 12-item Short Form Survey quality-of-life questionnaire (0–100, with higher scores indicating better quality of life). Another primary outcome was the reduction in pain as measured by the Patient Global Impression change (PGIC), where change in pain was rated on a 7-point scale, with lower scores representing a decrease in pain while higher scores represented an increase in pain. A baseline pain rating was obtained before initiation of treatment over three consecutive menstrual cycles. The OMT group had significantly lower pain levels after treatment (5.4 vs 2.0, $P<.001$) and mental component scores (52 vs 38, $P<.001$) compared with the control group (38 vs 52, $P<.001$). The OMT group showed a significant decrease in pain intensity compared with the decrease in the LTT group (3.37 vs 0.61, $P<.001$). Additionally, the final mean PGIC value for the OMT group was 2.2±1.1 ("very improved") while the final mean PGIC value for the LTT was 4.2±0.7 ("no change"). The study was limited by small sample size and narrow study population.

A 2014 RCT (n=60) evaluated the effectiveness of OMT in German women with pain related to primary dysmenorrhea.[2] Patients were diagnosed by their general practitioner or a gynecologist and had regular menstrual cycles. The mean age of the intervention group was 32 years old and that of the control group was 35 years old. Exclusion criteria included pregnancy, hormonal therapy, substance abuse, chronic illnesses, and a diagnosis of secondary dysmenorrhea. The intervention group (n=25) received six OMT treatment sessions over a course of three menstrual cycles. The OMT techniques used included High Velocity Thrust, Muscle Energy Technique, Myofascial Release, and indirect techniques such as Balanced Ligamentous Tension. The OMT treatments were not standardized and were chosen by the osteopathic physicians based on their structural examination findings. The control group (n=28) was untreated and put on a wait list. The primary outcomes measured were pain on a 10-point pain scale and duration of pain (measured in days). One secondary outcome was health-related quality of life measured by the SF-36 questionnaire (0–100 range, with higher scores indicating higher quality of life). Assessments were conducted at baseline (during the menstrual cycle before treatment was begun) and before and during four consecutive menstrual cycles during the intervention period of six months. The OMT group had significant reduction in menstrual pain after treatment compared with the control group (mean difference [MD] –2.6; 95% CI, –1.7 to –3.6). Additionally, a significant reduction was noted in duration of menstrual pain in the intervention group (MD –2.5 days; 95% CI, –1.6 to –3.5 days). No significant difference was noted in quality of life for the mental component, but a significant change was observed in the mean physical component score for the OMT group compared with the control group (MD –6.2; 95% CI, –1.2 to –11.1). Limitations of the study included lack of blinding, waitlist design, and study recruitment strategies. A low rate of dropout (4 from the intervention group and 3 from the

control group) was noted with reasons for dropout unrelated to the treatment. EBP

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Do long-acting inhaled anticholinergics provide any benefit to an asymptomatic patient with COPD?

EVIDENCE-BASED ANSWER

Use of once-daily inhaled tiotropium 18 μg (a long-acting muscarinic antagonist or LAMA) compared with placebo improves the forced expiratory volume in one second by 157 to 166 mL in patients with mild-to-moderate chronic obstructive pulmonary disease (COPD) when used for 12 weeks to two years (SOR: C, randomized controlled trials [RCTs]). The frequency of acute COPD exacerbations was slightly lower (by 0.23 events per person per year) in patients receiving tiotropium, although there was no improvement in quality-of-life measures. (SOR: B, RCT).

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In 2017, a RCT (N=771) evaluated the effects of tiotropium in patients with mild (forced expiratory volume in 1 second [FEV_1] ≥80% predicted) or moderate (FEV_1, 50 to <80% predicted) chronic obstructive pulmonary disease (COPD) as defined by Gold criteria.[1] Patients 40 to 85 years old, 85% male, with a median age of 64 years, were randomly assigned to receive a daily inhaled dose of tiotropium 18 μg or matching placebo for two years (N=388 and N=383, respectively). Median smoking index was comparable for both groups, ranging from 50 to 55 pack years. Baseline FEV_1 before bronchodilator use was 1.8 L in the placebo group and 1.8 L in the test group. Use of maintenance medications for COPD was avoided except if clinically necessary and initiated before the study. Patients who had a COPD exacerbation four weeks before the trial were excluded from the study, as well those with large airway disease, asthma, and severe systemic disease. The primary end point was the between-group difference in the change from baseline to 24 months in the FEV_1 before bronchodilator use. This study also analyzed the frequency of acute exacerbations of COPD between groups and the time to the first acute exacerbation. Tiotropium resulted in a significantly higher FEV_1 before bronchodilator use than placebo at 24 months (FEV_1 difference 157 mL; 95% CI, 123–192). The frequency of acute exacerbations of COPD was lower with tiotropium than with placebo (0.27 vs 0.50 events per patient per year; risk ratio [RR], 0.53; 95% CI, 0.39–0.73; $P<.001$). The time to the first acute exacerbation was longer with tiotropium than with placebo (522 vs 236 days; $P<.001$). Oropharyngeal discomfort was more common in the tiotropium group compared with placebo (15 vs 6.6%; $P<.001$). Limitations of this study include the fact that subjects selected did have baseline respiratory symptoms; thought these have been mild, subjects were not completely asymptomatic.

In 2008, a 12-week double-blind RCT (N=224) evaluated the efficacy of daily tiotropium 18 μg on lung function in patients with mild COPD as defined by 2003 Swedish guidelines (post-bronchodilator FEV_1/forced vital capacity <70%; FEV_1 ≥60% predicted).[2] This population is analogous to mild-to-moderate COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Patients 52 to 70 years old, 53% and 43% male, were randomly assigned to receive tiotropium (N=107) or placebo (N=117). Patients were required to have a smoking history of ≥10 pack years and a Medical Research Council (MRC) dyspnea score of ≥2 (out of 5).

Excluded from the study were those with asthma, allergic rhinitis, recent lower respiratory tract infection, any exacerbation in the previous six months, regular use of oxygen therapy, or the use of oral or inhaled steroids within the previous three months. The primary end point was the change in FEV_1 from a predose to two hours postdose from baseline to 12 weeks. Health-related quality-of-life outcomes were measured by the baseline dyspnea index (BDI) score (0–4; 0 very severe impairment, 4 no impairment) and the MRC dyspnea score. Results showed that the changes in FEV_1 from baseline to 12 weeks were significantly improved with tiotropium compared with placebo (157 vs –9 mL; difference, 166 mL; $P<.0001$). No significant differences were seen in health-related quality of life scores as assessed by the BDI and MRC scores. Quality-of-life assessments were limited by the short duration of this study and the lack of disease-specific instruments for assessment. EBP

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In women with dense breasts, does whole-breast ultrasound improve cancer detection compared with mammogram alone?

EVIDENCE-BASED ANSWER

The addition of whole-breast ultrasound to mammography for breast cancer screening in women with dense breasts finds 4.4 more cancers per 1,000 women compared with mammography alone; however, the false-positive rate for ultrasound is greater than 90% (SOR: **A**, systematic reviews). Expert opinion is mixed, but in general, most do not advise routinely adding ultrasound to breast cancer screening in women with dense breasts who have negative mammograms and no additional cancer risk factors (SOR: **C**, evidence-based and consensus guidelines).

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A 2016 systematic review identified two good-quality studies using hand-held ultrasonography as a supplemental screening modality for detecting breast cancer in women with negative mammograms and dense breasts.[1] Women were asymptomatic and defined as having dense breasts based on either the Breast Imaging Reporting and Data System, class c or d, or described as having heterogeneously or extremely dense breast parenchyma. In one study (n=1,216 with 3,414 examinations), women were on average 52.5 years old; in the other study (n=3,356 with 7,224 examinations), 55% were younger than 50 years old. Both trials were designed to determine test accuracy, using either biopsy results or follow-up for at least one year as a reference standard. Sensitivity of ultrasonography for detecting breast cancer in women with negative mammography results ranged from 80% (95% CI, 65%–91%) to 83% (95% CI, 59%–96%) and specificity from 86% (95% CI, 85%–88%) to 95% (95% CI, 94%–95%), with corresponding likelihood ratios (LRs) of 0.2 for LR negative and 5.9–16 for LR positive. Overall, ultrasonography found additional cancers in 4.4 (95% CI, 2.5-7.2) of 1,000 women screened; 89% of these cancers were invasive. However, between 92% and 97% of the abnormal ultrasound results in these two randomized controlled trials were false positives. Limitations of the studies included lack of information on breast cancer risk factors, as well as incomplete data on recall and biopsy rates.

A 2016 evidence-based recommendation statement on screening for breast cancer from the U.S.

Preventive Services Task Force found insufficient evidence to assess the benefits versus harms of adjunctive ultrasonography to detect breast cancer in women with dense breasts and negative mammograms (Grade I statement; insufficient evidence).[2] This statement was based in part on the previously mentioned systematic review.

A 2015 consensus opinion from the American College of Obstetricians and Gynecologists recommended against adding tests such as ultrasonography to screening mammography in women with dense breasts who have no symptoms and no additional risk factors (no strength of recommendation or grade provided).[3]

A 2017 consensus and evidence-based guideline from the American College of Radiology Committee on Appropriateness Criteria noted that mammography sensitivity may be as low as 50% in women with dense breasts and that adjunctive ultrasonography can significantly increase cancer detection rates (recommendation: may be appropriate in certain clinical scenarios, with general agreement among panel members).[4] However, the guideline also stated that false-positive rates increase substantially with breast ultrasonography and that no data existed to support breast ultrasonography for screening in women with dense breasts and average risk for breast cancer. EBP

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Is evolocumab a comparable alternative to statins in primary and secondary prevention of cardiovascular events in patients who cannot tolerate a statin?

EVIDENCE-BASED ANSWER

Evolocumab is well tolerated and reduces low-density lipoprotein cholesterol comparable with statins (SOR: **C**, disease-oriented evidence based on 2 randomized controlled trials [RCTs] and a meta-regression analysis). It also reduces major cardiovascular events compared with placebo (SOR: **B**, 1 RCT and a meta-regression analysis).

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A subset analysis of a randomized controlled trial of 27,564 patients looked to quantify cardiovascular outcomes in patients with peripheral artery disease (PAD) treated with evolocumab versus placebo.[1] The subset included 3,642 patients with symptomatic PAD with an ankle brachial index of less than 0.85 or who had a prior peripheral vascular procedure; 1,505 patients had no prior history of cardiovascular events. Before the study, 69% of patients were taking high-intensity statins, 30% were on moderate-intensity statins, and 6.6% were on ezetimibe. Patients remained on their baseline statin or ezetimibe during the trial. Patients were assigned 1:1 ratio of evolocumab (either 140 mg subcutaneously every 2 weeks or 420 mg subcutaneously every month) or placebo injections with

TABLE. LDL reduction and primary endpoint results (major cardiovascular events) for evolocumab[1]

Group (vs placebo)	% LDL-C reduction (95% CI)	Hazard ratio (95% CI)	Absolute Risk Reduction	Number Needed to Treat
PAD	59% (57–61)	0.79 (0.66–0.94)	3.5%	29
Non-PAD	NR	0.86 (0.80–0.93)	1.6%	63

LDL-C=low-density lipoprotein cholesterol; NR=not reported; PAD=peripheral artery disease.

a primary endpoint of major cardiovascular events and secondary endpoints of cardiovascular death, myocardial infarct, or stroke. At baseline, the study population had a median low-density lipoprotein cholesterol (LDL-C) level of 94 mg/dL. After 48 weeks of evolocumab therapy, the LDL-C level was reduced and resulted in a reduction in the primary endpoint in both the PAD and the non-PAD groups when compared with placebo (see **TABLE**). No serious adverse events were noted with evolocumab relative to placebo in patients with PAD (1.3% in evolocumab vs 1.5% in placebo, $P=.57$). A 27% reduction in secondary endpoint was noted (9.5% vs 13%; HR 0.73; 95% CI, 0.59–0.91). Although the study population was not selected for inclusion based on statin intolerance, the study did demonstrate the efficacy of evolocumab at reducing cardiovascular events. One limitation of this study was that while the PAD group was adequately powered for statistical significance in regards to the primary endpoint and key secondary endpoints, it was limited in the ability to detect rare safety events. Additionally, the limited duration of the trial may have reduced the chance of finding a significant reduction in cardiovascular deaths.

A 2014 double-blind randomized controlled trial enrolled 307 statin-intolerant patients to evaluate the efficacy and safety of evolocumab compared with oral ezetimibe.[2] The study was placebo and ezetimibe controlled, with a primary endpoint of change in baseline LDL-C. Patients were between 18 and 80 years old, had LDL-C levels above the National Cholesterol Education Program Adult Treatment Panel III criteria, and had previous intolerance to greater than or equal to two statins. Of the patients enrolled, 56% were deemed high risk for coronary heart disease. Baseline LDL-C in the control group (ezetimibe) was 195 mg/dL and evolocumab group 192 mg/dL. After 12 weeks, a mean LDL-C reduction of –105.4 mg/dL (biweekly regimen) and –103.6 mg/dL (monthly regimen) in the treatment arms and –39.6 and –30.2 mg/dL in the control arms was noted ($P<.001$). The incidence of treatment-emergent adverse events and laboratory abnormalities were comparable across treatment groups.

A meta-regression comparing the efficacy of multiple cholesterol-lowering regimens (statins, fibrates, and diet), included three randomized controlled trials (N=73,564) with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab, bococizumab and alirocumab) and their impact on risk reduction (RR) for stroke.[3] The multinational population evaluated across the trials were patients considered high risk based on prior vascular events (myocardial infarct, ischemic stroke, or symptomatic peripheral artery disease) or LDL levels greater than 70 mg/dL. An inverse variance-weighted linear regression method was used to extrapolate cholesterol reduction and the predicted stroke incidence for differing cholesterol medications. Total cholesterol reduction of 20%, 30%, and 40% would predict a RR of 0.85, 0.81, and 0.77, respectively, for stroke. For the PCSK9 inhibitors in the three trials, the predicted total RR for stroke fit a log-linear relationship and was 0.76, 0.76, and 0.85, respectively. This study is not a true meta-analysis, but instead focused on demonstrating a correlation between overall cholesterol lowering and RR of stroke; as such, the 95% CIs were not provided for the collective effect of PCSK9 inhibitors, and patient demographics were not included. EBP

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In community dwelling adults, does diet enrichment with fruit, vegetables, fish, and whole grains reduce the risk of new onset depression?

EVIDENCE-BASED ANSWER

A "healthy diet" is associated with reduction in odds for clinical depression (odds ratio: 0.84) while no statistically significant association is found between the typical "Western diet" and depression (SOR: **A**, systematic review and meta-analysis). In addition, adherence to healthy dietary recommendations reduces the risk of depressive symptoms while a "Western diet" increases the risk of depressive symptoms. (SOR: **A**, narrative systematic review)

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A 2014 systematic review of 21 studies addressing the association between dietary patterns and depression resulted in the selection of 13 observational studies for meta-analysis.[1,2] The inclusion criteria for selecting studies required the article to assess the entire diet, include depressive symptoms, depressive disorders or dysthymia as possible outcomes and enroll community-dwelling patients 18 years old or older. Articles were excluded if they examined only individual nutrients and not all of the dietary components, if they did not report depression data in an extractable format, or if they included patients that required nutritional needs different from the general population, as in pregnant or lactating women and athletes. Two main dietary patterns were identified: the healthy diet (described as high intake of fruit, vegetables, fish, and whole grains) and the Western diet (characterized by refined grains, processed meat foods or snacks, and high-sugar and high-fat products). The aggregated results of the meta-analysis, revealed that consumption of the healthy diet was associated with a statistically significant reduction in odds of depression (odds ratio [OR]: 0.84; 95% CI: 0.76–0.92; $P<.001$). In comparison, there was a trend towards a positive association between higher consumption of the Western Diet and the odds of depression, but this relation was not significant (OR: 1.17; 95% CI: 0.97–1.41; $P=.094$). A large number of the included studies (7 of 13) were cross-sectional in design, which limited their ability to show causality.

A 2020 narrative systematic review comprised of 22 studies investigated a diet's impact on depression (N=455,781).[1,2] These studies included two randomized controlled trials and several observational studies that all took place in Europe, Oceania, and the United States between 2012 and 2019. Studies regarding pregnant women and those in languages other than English were excluded. The review did not include information about how the studies obtained dietary information, but screening criteria for inclusion in the review included each papers' consideration for measurement methods and confounders. The authors identified several diet "categories" and outlined the associations of each category to depression and depressive symptoms. Overall, diets full of processed, pro-inflammatory, and high sugar containing foods (referred to as typically Western diets) were associated with higher risk of depression and more depressive symptoms while adherence to various dietary recommendations were found to have a protective effect against depression and depressive symptoms. A weakness of this study is that few randomized controlled trial studies were included in the result. EBP

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What types of exercise improve outcomes in adolescents with depression?

EVIDENCE-BASED ANSWER

Unclear. Physical activity such as aerobic exercise or resistance training may improve depression outcomes in adolescents at high risk for depression (SOR: **C**, mixed evidence from a meta-analysis and a systematic review). Combining physical exercise with education may further improve depression outcomes (SOR: **B**, meta-analysis).

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A 2013 meta-analysis (N=581) of five randomized controlled trials (RCTs), two controlled trials, one cluster RCT, and one quasi-experimental study examined the effect of physical activity treatments for depression in school-age adolescents 8 to 19 years old.[1] The majority of studies included patients deemed at high risk for depression. The majority of studies implemented aerobic exercise, with the other trials using yoga, different sports, and structured "physical fitness" classes. Length of trials ranged from 9 to 40 weeks. Duration of activity ranged from 20 to 90 minutes, with five of the studies carrying out sessions three days a week, the remaining studies had sessions ranging between 2 and 5 days. Depression outcomes were measured by various scoring systems, so results were pooled and converted to standardized mean difference (SMD). When compared with no physical activity, physical activity had a small, significant reduction in depression outcomes (9 trials, n=581; SMD –0.20; 95% CI, –0.39 to –0.01). Physical activity plus health education demonstrated a moderate reduction (4 trials, n=374; SMD –0.46; 95% CI, –0.75 to –0.17) compared with no physical activity.

A 2006 systematic review of 16 RCTs (N=1,191) looked at the impact of differing exercises in reducing or preventing anxiety or depression in adolescents between 11 and 19 years old.[2] Studies containing other psychological disorders such as psychosis or borderline behavior and those with physical disabilities were excluded. Interventions included walking, aerobics, or weight-lifting in addition to routine physical activity and were carried out for a minimum of four weeks. Comparison groups included children on a waiting list, nonexercise group, low-intensity exercise group, or psychological intervention alone. All outcomes were reported as SMDs because of variety in scoring measures. Only three studies looked at participants in treatment with a confirmed diagnosis of depression. In one small trial (n=11) comparing exercise with a control group of no treatment, no significant difference was noted between groups in depression improvement (SMD 0.78; 95% CI, –0.47 to 2.0). In two trials (n=70), aerobic exercise versus low-intensity or relaxation demonstrated no significant difference between the two groups (SMD –0.31; 95% CI, –0.78 to 0.16). In another trial (n=36), aerobic exercise versus psychosocial interventions demonstrated no significant difference between groups (SMD –0.31; 95% CI –0.97 to 0.35). None of the reviewed studies demonstrated a significant difference in depression scores between physical activity or the comparison groups. EBP

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In patients with chronic atrial fibrillation currently on warfarin, can INR surveillance be safely extended beyond four weeks?

EVIDENCE-BASED ANSWER

Patients on stable doses of warfarin for chronic atrial fibrillation can safely have their international normalized ratio (INR) monitoring extended to greater than five weeks and achieve a similar percentage of therapeutic INRs compared to monitoring every four weeks (SOR: **B**, single randomized controlled trial and cohort). However, extending INR surveillance beyond eight weeks may result in more patients with extreme INRs compared to an extension of 5 to 7 weeks (SOR: **B**, single cohort).

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A 2011 randomized controlled trial (n=250) examined the safety of extending international normalized ratio (INR) monitoring time to ensure patients on warfarin therapy stay in a target therapeutic range (TTR).[1] Patients (mean age 71 years old) in this one-year study were receiving long-term warfarin treatment with a TTR of 2.0 to 3.5 (depending on indication), had been managed by the study clinic for at least six months before enrollment, and maintenance doses of warfarin had been unchanged for the previous six months or longer. Patients were randomly assigned in a 1:1 ratio to a warfarin dose assessment schedule of every four weeks (n=126) or every 12 weeks (n=124) for 12 months. INR levels between 1.96 and 3.04 (target range of 2.0–3.0) and between 2.46 and 3.54 (target range of 2.5–3.5) were considered therapeutic. The TTR percentage was calculated from the time of randomization to the point of early withdrawal or end of the study. The primary outcome was the percentage of time in the TTR, both calculated and interpolated from monthly (and associated) INR results. For each patient, the TTR percentage was calculated between successive INR test results, with the number of days in the therapeutic range estimated for the number of days the patient was in the study over the year. After randomization, all patients were assigned to one of the two groups, and all were scheduled for INR tests every four weeks for one year. For patients randomly assigned to warfarin dosing assessment every four weeks, *true* INR results were reported. Those patients assigned to dose assessment every 12 weeks were in a *separate* randomization process allocated to have one of the first three true INR results reported every four weeks consistently throughout the year; the other two results were reported as sham values of 1.8 to 3.5 for patients with a TTR of 2.0 to 3.0 or 2.0 to 4.0 for patients with a therapeutic INR range of 2.5 to 3.5. The range of sham values outside of the TTR was intended to maintain stable warfarin dosing based on studies demonstrating that an INR modestly outside the therapeutic range in otherwise stable patients will probably fall within the therapeutic range again by continuing the same warfarin dose. Sham extreme INR results (1.5% of all INRs) in the 12-week group were reported unblinded as it would be unethical not to inform the investigator of the extreme results, particularly for high INRs. There was no significant difference between the mean TTR percentage of the four-week group compared to the 12-week group (74% vs 72%, noninferiority $P=.02$). No significant differences between the treatment group and TTR percentage were found among subgroups defined by INR therapeutic range, sex, use of antiplatelet agents, heart failure, or diabetes mellitus.

A 2018 prospective cohort study (N=4,094) assessed the frequency and safety of clinical providers recommending an extended INR testing interval (>5 weeks) to eligible patients.[2] Stable warfarin patients, identified as those who did not require weekly dose changes and had goal INR values for greater than 12 weeks to greater than six months, qualified for extended interval monitoring. Patients who self-monitored INR, had a left ventricular assist device, had chronic renal insufficiency, or experienced a clinically significant adverse event such as an emergency department visit, or bleeding event were excluded.

Patient follow-up was determined by each clinic and ranged from 6 to 8 weeks from first INR testing. The study included 2,479 patients in the extended INR testing group and 1,615 patients in the standard monitoring group. Outcomes measured included total follow-up time, out-of-range INRs, extreme INRs, bleeding events, emergency department visits, and thromboembolic events. There was no significant difference in the number of out-of-range INR values for the standard follow-up group compared to the extended follow-up group (17% vs 28%, $P=.46$), or in extreme INR values (6.4% vs 7.7%, $P=.11$).

However, patients with a follow-up INR in 5 to 7 weeks compared to patients with follow-up INRs in greater than eight weeks had statistically significantly fewer extreme INRs (5.5% vs 9.3%, $P=.001$). Bleeding events were similar between groups, and no thrombotic events occurred. EBP

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