September 2023

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

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FPIN
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A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

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EVIDENCE-BASED PRACTICE

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STATEMENT OF PURPOSE

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

EDITORIAL POLICY

DISCLOSURE

The PURLs Surveillance System is supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

One toaster for all

I work in the southern, low-income part of town. My patients are working multiple jobs, insist their children get vaccinated, and almost never ask about gluten elimination diets. I have a friend in private practice who works in the northern, high-income part of town. His patients work at software jobs, often refuse to get their children vaccinated, and suffer widely from gluten "sensitivity."

I am not sure what is happening up north that makes gluten so irritating when it is a nutritious food staple down here. But, tipping my hat to vagaries of epidemiology, I allow that some patients are severely disabled by gluten enteropathy and need to go to great lengths to prevent cross-contamination of what they eat with stray gluten which is ubiquitous in our food culture and our kitchens.

Fortunately, recent research suggests that gluten cross-contamination is not quite as inevitable in the kitchen as might be anticipated. A group of researchers decided to perform various common food preparation tasks (toasting bread, slicing cupcakes, and cooking pasta) first with a gluten-containing food and then with a gluten-free food and to assay the level of gluten transfer. They defined contamination as the appearance of gluten above 20 parts per million, since levels below this are the standard for a "gluten free" designation.

Using the same toaster did not result in contamination when gluten-containing and gluten-free breads were alternated. Contamination also did not occur when cutting cupcakes if the knife was washed between uses. Even if the knife was not even wiped off (retaining a smear of frosting and tiny crumbs), cupcake cross-contamination at a level of 20 ppm only occurred in only two of 28 tests. Finally, so long as a pasta cooking pot was simply rinsed with water between uses, pasta cross-contamination did not occur at any level.

This is great news for folks with debilitating gluten enteropathy (as well as all the family members of people up north claiming gluten "sensitivity"). If their kitchens are anything like mine, there really is not room for two toasters.

Jon O. Neher

DOI 10.1097/EBP.0000000000001999

Reference

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Thank You Peer Reviewers

Peer review is integral to scholarly writing, and ensuring evidence-based medicine is used in primary care. FPIN would like to thank all individuals who have volunteered their time and talents in providing feedback to the authors of our journal, *Evidence-Based Practice*.

Thank you to all our 2022-2023 academic year peer reviewers! You are appreciated!

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Should low-risk pregnancies last longer than 40 weeks?

Muglu J, Rather H, Arroyo-Manzano D, et al. Risks of stillbirth and neonatal death with advancing gestation at term: A systematic review and meta-analysis of cohort studies of 15 million pregnancies. *PLoS Med*. 2019; 16(7): e1002838.

DOI 10.1097/EBP.0000000000001038

This systematic review and meta-analysis examined studies looking for the optimal time to induce labor to minimize risk of stillbirth while not increasing neonatal death. Thirteen studies (N=15,124,027) met inclusion criteria by studying the rates of stillbirth or neonatal death at various gestational ages among groups of women at low risk for pregnancy complications. The studies included patients from the United States (74%), Norway (11%), the United Kingdom (10%), and Denmark (5%). Women of White, Black, and Asian races were included. The authors were unable to determine other demographic data such as age, socioeconomic status, or parity from the included meta-analyses. Exclusion criteria were preexisting medical conditions such as preeclampsia, gestational diabetes, or small for gestational age fetuses. The authors calculated the week-specific prospective risk of stillbirth and neonatal death using a validated logistic regression model. They then compared the change in week-specific risk of either event between two given weeks to obtain a risk ratio. The risk of stillbirth increased for each week between 37 and 42 weeks. The stillborn risk increased from 0.69 per 1,000 deliveries at 40 weeks to 1.66 per 1,000 deliveries at 41 weeks. The risk of neonatal death between 38 and 41 weeks was not increased. Although clearly robust in total number of participants, study quality was limited by lack of a standardized definition of low-risk pregnancy, heterogeneity in exclusion of medical problems, inclusion of studies spanning 32 years, and moderate risk of publication bias. The authors concluded that significant risk of stillbirth exists when pregnancies are extended to 41 weeks when compared with delivery at 40 weeks without any corresponding increased risk of neonatal death. These findings were consistent with the ARRIVE trial that looked at induction versus expectant management of labor at 39 weeks.[1] In addition to the primary endpoint of neonatal death, this ARRIVE trial also found no increase in risk of severe neonatal morbidity or maternal morbidity among women induced at 39 weeks.

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

Bottom line

Among women with low-risk pregnancies, delivery at 40 weeks significantly reduces the risk of stillbirth when compared with delivery at 41 weeks.

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The author declares no conflicts of interest.

Reference

1. Grobman WA, Rice MM, Reddy UM, et al. Labor induction versus expectant management in low-risk nulliparous women, *New Engl J Med.* 2018; 379:513–523.

Does it matter how I get the steroid?

Citation: Wang Q, Mol MF, Bos PK, et al. Effect of Intramuscular vs Intra-articular Glucocorticoid Injection on Pain Among Adults With Knee Osteoarthritis: The KIS Randomized Clinical Trial. *JAMA Netw Open*. 2022;5(4): e224852. Published 2022 Apr 1. https://doi:10.1001/jamanetworkopen.2022.4852

DOI 10.1097/EBP.0000000000001852

A Dutch open-labeled, parallel, randomized controlled, noninferiority multicenter clinical trial investigated intramuscular (IM) verses intra-articular (IA) glucocorticoid injection for symptomatic knee osteoarthritis (OA) over a 24-week period with investigators blinded but neither patients nor clinicians blinded. Patients were adults 45 years of age or older seen in primary care for knee symptoms diagnosed as osteoarthritis by a general

practitioner, with the presence of symptomatic OA for at least 3 months and moderate to severe pain (rated ≥3 on a pain scale of 0–10) over the previous week. Patients were excluded if they had a glucocorticoid injection within the past 6 months, had type 1 or poorly controlled type 2 diabetes mellitus, or had a recent gastric or duodenal ulcer. Each group received a 40 mg triamcinolone acetonide injection either IM in the ipsilateral ventrogluteal region or IA in the affected knee joint. The primary outcome was the pain score at 4 weeks after injection measured with the Knee Injury and Osteoarthritis Outcome Score (KOOS; range 0–100 with 0 indicating the most severe pain).

Researchers enrolled 145 patients (65% women, average age 67 years) in the intention-to-treat group with 74 IM patients and 71 IA patients, respectively. At 4 weeks, the estimated mean difference (MD) in KOOS pain scores between the two groups was –3.4 (95% CI, –10.1 to 3.3). The preselected acceptable noninferiority margin was –7, and because the CI included –10.1, noninferiority was not established. Secondary outcomes included KOOS pain scores at 2, 8, 12, and 24 weeks with noninferiority noted at 8 and 24 weeks (MD, 0.7; 95% CI, –6.5 to 7.8 and MD 1.6; 95% CI, –5.7 to 9.0, respectively). Other secondary outcomes used a variety of outcome tools to measure symptoms, function, stiffness, and quality of life with no significant difference in secondary outcome improvement in either group. Mostly mild adverse events were reported in 24 of the IM patients (33%) and 28 of the IA patients (42%) with most frequent complaints being hot flushes 7 (10%) in IM and 14 (21%) in IA and headache 10 (14%) in IM and 12 (18%) in IA. Severe allergic reactions were uncommon: 2 in IM and 1 in IA. Noninferiority of IM to IA injection was not established at the primary endpoint of the pain score at 4 weeks. IM injection was also not established as noninferior at 2 and 12 weeks, but noninferiority was established at the 8- and 24-week follow-ups.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching UpToDate and Dynamed with the terms "injections for knee osteoarthritis," "knee osteoarthritis," and "Kenalog" to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: The 8- and 24-week effect of IM steroid injection was shown to be noninferior to IA injection for knee pain, whereas noninferiority was not established at 2, 4, and 12 weeks. Validity is questionable, given different results throughout the time intervals.

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The authors declare no conflict of interest.

Don't wait! Treatment for mild chronic hypertension in pregnancy

Tita AT, Szychowski JM, Boggess K, et al. Treatment for mild chronic hypertension during pregnancy. N Engl J Med. 2022;386(19):1781-1792. doi:10.1056/NEJMoa2201295

DOI 10.1097/EBP.0000000000001834

In an open-label randomized controlled trial conducted at over 70 sites in the United States, pregnant patients with chronic hypertension and singleton fetuses at gestational age less than 23 weeks were randomized to active treatment of hypertension or standard treatment in which blood pressure medication was withheld unless blood pressure reached 160/105 mmHg. Patients were excluded if they had severe hypertension at randomization, known secondary hypertension, certain high-risk comorbidities like cardiac or renal disease, fetal anomaly, or suspected intrauterine growth restriction. For both groups, first-line medications were labetalol or nifedipine ER. The blood

pressure goal in the active-treatment group was <140/90 mmHg, whereas goal of the standard-treatment group was <160/105 mmHg. Patients were followed until six weeks after delivery. The primary outcome was a composite of fetal or neonatal death before 28 days of life, superimposed preeclampsia with severe features up to two weeks postpartum, placental abruption leading to delivery, and medically indicated preterm birth at less than 35 weeks' gestation. Safety outcomes included birthweight at less than 10th and less than fifth percentile for gestational age. Outcomes are reported for complete case analyses, which did not differ from intention-to-treat analysis. Primary outcome events occurred in 30.2% of the active-treatment group compared with 37% of the standard-care group through six weeks postpartum (adjusted risk ratio [aRR] 0.82; 95% CI, 0.74–0.92; $P<.001$; number needed to treat=15). Preeclampsia with severe features occurred less often in the active-treatment group compared with the standard-treatment group (23.3% vs 29.1%; aRR 0.80; 95% CI, 0.70–0.92) as did medically indicated preterm birth before 35 weeks (12.2% vs 16.7%; aRR 0.73; 95% CI, 0.6–0.89). There was no difference in rates of placental abruption, fetal or neonatal death, or infant birth weights less than 10th or fifth percentile for gestational age.

Methods

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

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

Bottom line: Treatment of chronic hypertension during pregnancy to a blood pressure target of <140/90 mmHg (compared with a goal of <160/105 mmHg) is associated with improved outcomes and no increased risk of infants born small for gestational age.

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The authors declare no conflicts of interest.

When should bone mineral density testing be repeated in patients with osteopenia not on bisphosphonate therapy?

EVIDENCE-BASED ANSWER

Repeat bone mineral density (BMD) testing for postmenopausal women with mild, moderate, and severe osteopenia at intervals of 17, five, and one year respectively is required for 10% of women in each category to transition to osteoporosis. (SOR: **C**, single prospective, observational study). Repeat BMD testing three years after baseline testing does not predict women who will eventually experience a hip or major osteoporotic fracture better than baseline BMD testing alone (SOR: **C**, single prospective, observational study).

DOI 10.1097/EBP.0000000000001842

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2012 prospective, longitudinal study (n=4,957) conducted a competing risk analysis to assess the time it would take for postmenopausal women to transition from normal bone mineral density (BMD) or osteopenia (T score –1 to –2.49) to osteoporosis (T score –2.5 or lower).[1] Researchers evaluated postmenopausal women 67 years old or older recruited from four sites in the US. Patients without osteoporosis on baseline BMD testing and no history of osteoporosis treatment, hip or vertebral fracture were included. Women with bilateral hip replacements were excluded. After initial BMD testing, follow up consisted of serial BMD testing of the femoral neck and total hip for up to 15 years. The primary outcome was the estimated time it would take for 10% of women to transition from normal BMD or osteopenia to either osteoporosis before hip or vertebral fracture or initiation of osteoporosis treatment. The estimated time for repeat BMD testing was 17 years for normal BMD based on T score of –1 or higher (95% CI, 12–25), 17 years for mild osteopenia based on T-score of –1.01 to –1.49 (95% CI, 14–21), 4.7 years for women with moderate osteopenia based on T-score of –1.5 to –1.99 (95% CI, 4.2–5.2), and 1.1 years for women with severe osteopenia based on T-score of –2 to –2.49 (95% CI, 1–1.3). This study was limited by including only older postmenopausal women and greater than 99% of the cohort being Caucasian. It did not consider factors such as risks and benefits of screening and cost-effectiveness.

A 2020 prospective, longitudinal study (n=7,419) analyzed whether repeat BMD testing three years after baseline assessment estimated fracture risk better than baseline measurement alone.[2] Researchers analyzed postmenopausal women 50 to 79 years old (mean age 66 years) from three sites in the US. Patients had no past history of osteoporosis treatment or major osteoporotic fracture. Women with serious cardiac, pulmonary, renal and hepatic conditions were excluded. Patients underwent baseline BMD testing with repeat testing three years later and were then followed for an average of nine years afterwards. Patients reported hip fractures and major osteoporotic fractures (defined as hip, spine, radius, ulna, wrist, upper arm or shoulder fracture) via self-reported annual questionnaires. A Cox proportional hazards regression calculated an area under the receiver operative curve (AU-ROC) to compare the diagnostic accuracy of baseline and repeat BMD testing at three years. As a diagnostic tool, an AU-ROC increases in diagnostic accuracy as it approaches 1.0, with a value of 0.5 corresponding to random chance. Analysis failed to find a difference between baseline total hip BMD (AU-ROC 0.71; 95% CI, 0.67–0.75), change in total hip BMD on repeat testing (AU-ROC 0.61; 95% CI, 0.56–0.65), and combination of baseline and change in BMD on repeat testing (AU-ROC 0.73; 95% CI, 0.69–0.77) at predicting hip fracture. Similarly, there were no differences in baseline and repeat BMD testing at three years at predicting other major osteoporotic fractures. Limitations included the possibility of residual confounding factors due to the observant nature of the study and reliance on self-reported fractures. EBP

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

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1. Gourlay ML, Fine JP, Preisser JS, et al. Bone-density testing interval and transition to osteoporosis in older women. *N Engl J Med.* 2012; 366(3):225-233. [STEP 3]

2. Crandall CJ, Larson J, Wright NC, et al. Serial bone density measurement and incident fracture risk discrimination in postmenopausal women. *JAMA Intern Med.* 2020; 180(9): 1232-1240. [STEP 3]

Weighted blankets for chronic pain, the jury is out: Erratum

In the article that appeared on page 3 of the December 2022 issue of *Evidence-Based Practice*, entitled "Weighted blankets for chronic pain, the jury is out" there was an error. The sentence "Use of weighted blankets produced no statistically significant reduction in pain" was incorrect. The correct sentence is "For the primary outcome, use of weighted blankets produced no statistically significant reduction in pain via VAS rating."[1]

Reference

1. Earwood J, Conner SJ, Perdue JG. Weighted blankets for chronic pain, the jury is out. *Evidence Based Practice.* 25(12):3. doi. 10.1097/EBP.0000000000001680

In patients with concussion symptoms, do SSRIs aid in recovery?

EVIDENCE-BASED ANSWER

It is not clear. SSRIs may moderately improve the symptoms of depression in patients who have suffered a concussion (SOR: **B**, meta-analyses not limited to randomized controlled trials).

DOI 10.1097/EBP.0000000000001893

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2017 meta-analysis and systematic review examined the utility of SSRIs in treating neurocognitive and neuropsychiatric disorders after a traumatic brain injury.[1] Studies included eight randomized controlled trials (RCTs), nine open-label studies, 11 case reports, and nine narrative review articles (N=796). A subset of two small RCTs compared sertraline 25 mg daily titrated to 100 mg daily with placebo treating depression after a traumatic brain injury. Traumatic brain injury included mild-to-moderate concussion, and the mechanism of injury was not specified. Patients were evaluated with the Hamilton Depression Scale (Ham-D; scored 0–52, with higher scores indicating greater symptoms). Sertraline moderately decreased depression burden in patients after traumatic brain injury (TBI) compared with placebo (2 RCTs, N=61; effect size of treatment –0.67; 95% CI, –1.19 to –0.16). A subset of one RCT (n=99) and one prospective cohort study (n=54) evaluated SSRI for postconcussive symptoms. The RCT studied sertraline dosed 25 to 100 mg daily for four weeks compared with placebo, and the open-label prospective cohort study investigated citalopram with a starting dose of 20 mg/day to a maximum of 50 mg/day (no comparison group) for 6 to 10 weeks. The primary outcome in both studies was the Rivermead Post-Concussive Symptoms Questionnaire (RPQ), a 16-item instrument scored from 0 to 4 where higher scores indicate worse symptoms. No significant change was observed in RPQ scores in either group in the RCT. Patients treated with citalopram in the prospective cohort study reported a decrease in RPQ scores at six weeks (n=54; 15.4–11.4; $P<.0001$). Harms of the intervention included interactions with other psychotropic medications, akathisia, and sexual dysfunction (statistical significance not reported).

A 2021 systematic review examined associations between commonly used pharmacological interventions and symptom burden reduction among patients with mild TBI (11 RCTs, 7 prospective cohort studies, 3 retrospective cohort studies, and 2 case studies; N=8,322).[2] Studies were excluded if they had an inadequate definition of TBI or included intracerebral hemorrhage. Two prospective cohort SSRI studies not included in the 2017 meta-analysis (N=30) evaluated the effect of sertraline 25 to 200 mg daily for eight weeks on depression symptoms using the Ham-D scale and concussion symptoms using the self-reported Head Injury Symptom Checklist. In treated patients, the mean Ham-D score at the end of the eight-week treatment phase declined from baseline (baseline not given; –7.2 points; $P<.001$). Evaluation of postconcussive symptoms using the Head Injury Symptom Checklist in the cohort study showed an improvement compared with baseline with an average of 48% of patients reporting improvement in each of the categories assessed. Limitations of the systematic review included a moderate risk of bias and industry funding in both cohort studies. High heterogeneity precluded meta-analysis and limited generalizability. EBP

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The author team declares no conflict of interest.

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1. Yue JK, Burke JF, Upadhyayula PS, et al. Selective serotonin reuptake inhibitors for treating neurocognitive and neuropsychiatric disorders following traumatic brain injury: an evaluation of current evidence. *Brain Sci.* 2017; 7(12):93. [STEP 1]
2. Feinberg C, Carr C, Zemek R, et al. Association of pharmacological interventions with symptom burden reduction in patients with mild traumatic brain injury: a systematic review. *JAMA Neurol.* 2021; 78(5):596–608. [STEP 2]

What are the benefits and risks of aspirin as primary prophylaxis for CAD events?

EVIDENCE-BASED ANSWER

Aspirin reduces the risk of certain cardiovascular (CV) outcomes (including CV mortality and nonfatal myocardial infarction) when used as primary prevention; however, the risk of bleeding with aspirin is nearly equivalent to the CV risk reduction (SOR: **A**, systematic reviews and meta-analyses of randomized controlled trials). Multiple organizations recommend shared decision making for each patient when primary prevention with aspirin is being considered (SOR: **C**, consensus statements).

DOI 10.1097/EBP.0000000000001899

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2019 systematic review and meta-analysis examined 13 randomized controlled trials (RCTs) that compared cardiovascular (CV) outcomes using primary prevention with aspirin versus no aspirin (placebo or no treatment).[1] A total of 164,225 patients were included in the meta-analysis, with a median age of 62 (range 53–74) years old. The primary outcome was a composite of CV mortality, nonfatal myocardial infarction (MI), and nonfatal stroke. Major bleeding was an additional primary outcome. Definitions of major bleeding included severe gastroenterology (GI) bleeding, hemorrhagic stroke requiring hospital admission, or severe bleeding requiring transfusion, but the exact definition of major bleeding varied among studies. RCTs were considered eligible for meta-analysis if they enrolled patients without known pre-existing CV disease; compared aspirin at any dose with no aspirin; had a follow-up of at least 12 months; enrolled over 1,000 patients; and provided information on any of the prespecified CV, bleeding, or cancer outcomes. Patients with diabetes comprised 18.5% of the total patient population undergoing meta-analysis, and three trials exclusively enrolled patients with diabetes. Because a Bayesian meta-analysis was used, results were presented as hazard ratios (HRs) with 95% credible intervals (CrIs). The aspirin cohort had a reduced risk of the primary composite CV outcome (60.2 per 10,000 participant-years) compared with no aspirin (65.2 per 10,000 participant-years; HR 0.89; 95% CrI, 0.84–0.94; number needed to treat [NNT]=241). Aspirin also increased the risk of major bleeding (HR 1.43; 95% CrI, 1.30–1.56; number needed to harm [NNH]=210). This decrease in primary CV composite outcome and increase in major bleeding was consistent across studies in populations with low and high CV risk and in studies that specifically examined risk in patients with diabetes. Limitations included the wide period covered by the studies (some patients were randomized as early as the 1970s), with changing standards of care. Hemorrhagic stroke was considered a bleeding outcome but could also be considered a CV event. Finally, the total daily dose of

TABLE. Cardiovascular and bleeding outcomes with aspirin for primary prevention compared with placebo

Outcome	Number of trials	Number of patients	Incidence (%)	RR (95% CI)	Magnitude
MI					NNT
All MI	15	165,502	2.07 vs 2.35	0.85 (0.75–0.95)	357
Nonfatal MI	14	161,791	1.37 vs 1.62	0.82 (0.72–0.94)	400
Bleeding					NNH
Major bleeding	11	157,865	1.47 vs 1.02	1.50 (1.33–1.69)	222
Intracranial bleeding	12	160,404	0.42 vs 0.32	1.32 (1.12–1.55)	1,000
Major GI bleeding	10	143,401	0.80 vs 0.54	1.52 (1.34–1.73)	385

GI=gastroenterology; MI=myocardial infarction; NNH=number needed to harm; NNT=number needed to treat; RR=risk ratio.

aspirin varied, including some doses that are not regularly used in current practice (such as doses >100 mg daily).

Another 2019 systematic review and meta-analysis of 15 RCTs also studied clinical outcomes for primary prevention of CV events with aspirin versus control.[2] Twelve studies from this meta-analysis were also included in the aforementioned meta-analysis. A total of 165,502 patients were included, with a mean age of 62 years old. Trials were eligible for inclusion if they compared aspirin at any dose with control or placebo and reported outcomes at a minimum follow-up of one year. Studies were excluded from meta-analysis if they included patients with active CV disease, compared aspirin to any active control, or combined aspirin with other antiplatelet or antithrombotic medications (unless separate data were reported for aspirin-only treatment groups). The key efficacy outcome was major adverse cardiac events (MACE) that included all-cause death, CV death, MI, and major adverse CV events. Safety outcomes included major bleeding (defined as requiring transfusion, needing hospital admission, or fatal bleeding events), intracranial bleeding, fatal bleeding, and major GI bleeding. Rates of all-cause death and non-CV death were similar between groups. The aspirin cohort had a lower risk of MI versus control. The risk of nonfatal MI was reduced in the aspirin group, but the risk of fatal MI was similar between groups. Regarding bleeding outcomes, aspirin increased the risk of major bleeding, intracranial bleeding, and major GI bleeding. The authors also noted that higher doses of aspirin (≥300 mg/day) conferred a higher risk of total stroke (**TABLE**).

The U.S. Preventive Services Task Force (USPSTF) recommendations from 2022 recommended aspirin as primary prophylaxis for CV disease in patients 40 to 59 years old with a 10% or greater 10-year ASCVD risk, but noted that the decision should be individualized because the net benefit is small. The USPSTF recommended against initiating aspirin as primary prevention in patients 60 years old and older.[3]

Similarly, the 2019 American College of Cardiology/American Heart Association (ACC/AHA) guidelines stated that aspirin could be considered for primary prevention in select patients 40 to 70 years old with higher risk of CV disease. The ACC/AHA recommended against using aspirin as primary prevention in patients >70 years old or in any patient with increased bleeding risk.[4] EBP

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In adults with depression, does the addition of chronotherapy to standard therapy result in decreased depressive symptoms compared to standard therapy alone?

EVIDENCE-BASED ANSWER

Total sleep deprivation (SD) as adjunctive therapy to standard therapy does not reduce depressive symptoms when compared with standard therapy alone (SOR: **B**, meta-analysis randomized controlled trials [RCTs] and a cohort study). SD, when combined with a broader range of adjunctive traditional and chronotherapy modalities, also does not improve depressive symptoms at one, two, and four weeks or three months compared with controls without SD (SOR: **B**, meta-analyses of RCTs).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 meta-analysis of six randomized controlled trials (RCTs; N=215) and one cohort study (n=49) compared total sleep deprivation (SD) combined with standard treatment versus standard treatment alone for treatment of depression.[1] The studies included adult patients with unipolar or bipolar depression according to DSM-V criteria. Mean ages ranged from 33 to 71, with one study including only elderly patients (mean age 70–71 years old). Two studies were performed in the outpatient setting. Standard treatment included antidepressants and cognitive behavioral therapy. Duration of treatment was one week, with follow-up differing between two to nine weeks. The primary outcome was depressive symptoms as measured by the Hamilton Depression Rating Scale (HDRS), a 17-item questionnaire with a maximum of 52 points, with increasing scores indicative of worsening depression. Included studies used differing total SD protocols, and two studies combined total SD with other chronotherapeutic interventions (light therapy and sleep time stabilization). Depressive symptoms were assessed using the HDRS questionnaire at baseline and throughout the study durations. Pooled analysis revealed no difference in depressive symptoms between total SD as adjunctive treatment and standard treatment alone within the first week of treatment or at any follow-up interval. Limitations of this meta-analysis included variance between treatment protocols, pretreatment diagnoses, concurrent treatments, and versions of the HDRS used. This meta-analysis also lacked pretreatment assessments.

A 2022 meta-analysis and systematic review of 29 RCTs (N=1,246) compared SD combined with other interventions versus control interventions in the treatment of major depressive episodes.[2] The interventions included pharmacological antidepressants, exercise, and chronotherapy methods such as partial sleep restriction, light therapy, sleep advice, and other forms of SD. The studies included patients with an ongoing unipolar or bipolar depressive episode (definition varied depending on RCT). This analysis did not specify an age limit or contain a language restriction. Mean age was 42 years old (range 15–72 years old). RCTs took place in an outpatient (3), inpatient (17), or combined outpatient and inpatient setting (7). One study did not report their setting. Mean duration of treatment was one week (range 1 day to 6 months). Primary outcomes included reduction in depressive symptoms and total number of patients who experienced at least one side effect. Reduction in depression symptoms was defined as the mean endpoint scores in depression severity from baseline to a specified follow-up point in each study (range 1 day to 29 weeks). Depression severity was most frequently measured by full or abbreviated versions of the HDRS but also included various other validated depression rating scales across RCTs. Included studies used both partial and total SD protocols. Eight studies used SD protocols in both treatment arms. Eighteen studies included medications. Of the 18 studies (N=705) included in the meta-analysis, no difference in depressive symptoms was noted in the SD group compared with the same intervention without SD at one, two, and four weeks and three months. A secondary sensitivity analysis of all 29 studies (including all studies even if SD could not be separated from other treatment modalities) was mixed; it favored a slight improvement of depressive symptoms with SD at one week (standardized mean difference [SMD] –0.46; 95% CI, –0.7 to –0.21) and three months (SMD –0.55; 95% CI, –1 to –0.09), but not at 24 hours, 72 hours, two weeks, and four weeks. No difference in the number of adverse events was reported. Limitations of this review include use of SD in both treatment arms of multiple studies, low quality of included studies, variance in treatment protocols, and use of different symptom severity scales. EBP

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What are the potential side effects and long-term risks of tenofovir disoproxil fumarate /emtricitabine compared with placebo for HIV pre-exposure prophylaxis?

EVIDENCE-BASED ANSWER

HIV pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF)/emtricitabine (Truvada) is associated with a modest increased risk of non-severe renal and gastrointestinal adverse effects (number needed to harm of 179 and 51, respectively) but not severe adverse events (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). TDF-based PrEP decreases bone mineral density by an average of 0.82% but does not increase the risk of fracture (SOR: **A**, meta-analysis of RCTs).

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A 2019 meta-analysis of 14 randomized controlled trial (RCTs; N=18,837) summarizing evidence of harms and benefits of pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF)/emtricitabine included nine RCTs specifically investigating adverse effects.[1] The studies included adults with high-risk sexual practices or injection drug use (mean ages 24–37 years old). Pregnant patients were excluded. In eight studies, patients received either TDF/emtricitabine (300 or 200 mg once daily) or placebo. One study compared immediate TDF/emtricitabine (245/200 mg once daily) with TDF/emtricitabine deferred by one year. Study duration ranged from four months to four years. Studied adverse outcomes included decreased renal function (defined as creatinine increase >0.3 mg/dL or 1.5–1.9 times baseline), gastrointestinal side effects, fractures, and serious adverse events (not defined by the review). Compared with placebo, PrEP with TDF/emtricitabine increased the risk of renal adverse events (9 RCTs, N=14,651; relative risk [RR] 1.5; 95% CI, 1.2–2.0; number needed to harm [NNH]=179) and nausea (9 RCTs, N=14,651; RR 1.8; 95% CI, 1.3–2.7; NNH=51). TDF-based PrEP did not increase the risk of serious adverse events (9 RCTs, N=14,651; RR 1.0; 95% CI, 0.8–1.3), discontinuation of medicine because of side effects (4 RCTs, N=9,704; RR 1.3; 95% CI, 1.0–1.6), or fractures (6 RCTs, N=12,387; RR 1.1; 95% CI, 0.7–1.7). Limitations included substantial variability between the studies in medication formulation, medication dose, medication adherence, population studied, exposure risk, and duration of study.

A 2020 meta-analysis of 10 RCTs (N=10,989) evaluated the effect of TDF-based PrEP regimens on bone mineral density (BMD) and related outcomes.[2] Four of these studies overlapped with the above review. The trials included adults (>18 years old) with high-risk sexual practices or injection drug use. No exclusion criteria were stated. TDF-based PrEP regimens included either TDF/emtricitabine (300 mg/200 mg, 7 RCTs) or tenofovir alone (300 mg, 3 RCTs). Nine RCTs evaluated daily medication regimens and one study looked at on-demand PrEP. The comparator for all trials was placebo. Primary outcomes included the change in BMD of the lumbar spine and hip, and the incidence of osteoporosis. Outcomes were assessed after a minimum of 48 weeks. TDF-based PrEP regimens were associated with a decrease in BMD in the lumbar spine (4 RCTs, N=1,347; mean difference [MD] −0.82%; 95% CI, −1.3 to −0.37%) and hip (4 RCTs, N=1,347; MD −0.81%; 95% CI, −1.2 to −0.4%). One year after discontinuing PrEP, BMD increased by 1.8% at the spine and 1.1% at the hip (1 RCT, n=498, *P*=.003). TDF-based PrEP did not increase fracture risk (5 RCT, N=6,552; RR 1.1; 95% CI, 0.75–1.7). Limitations included variability in medication selection, dose, dosing schedule, type and frequency of bone density testing. EBP

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What is the dietary recommendation for protein in patients who have chronic kidney disease?

EVIDENCE-BASED ANSWER

In patients with chronic kidney disease stages 3 to 5 without diabetes, a very-low-protein diet reduces the progression to end-stage renal disease (ESRD) but does not reduce mortality (SOR: **A**, meta-analysis of randomized controlled trials). Restricted dietary protein intake is recommended to help decrease the risk ESRD and perhaps improve quality of life (SOR: **B**, evidence-based guidelines).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

In 2018, a meta-analysis consisting of 17 randomized controlled trials (RCTs) and quasi-RCTs (N=2,996) compared the efficacy of a low-protein diet with a normal diet in patients with chronic kidney disease (CKD) in preventing progression to end-stage renal disease (ESRD) or dialysis.[1] The review was limited to studies with a minimum of 12 months' duration and included patients with CKD stage 3 to stage 5, but excluded those with diabetes mellitus, on dialysis, or with a history of kidney transplant. Researchers compared diets consisting of normal protein intake (≥0.8 g/kg/day), low-protein intake (0.5–0.6 g/kg/day), and very-low-protein intake (0.3–0.4 g/kg/day) for 12 to 50 months. There was no difference in mortality (5 studies, N=1,680; relative risk [RR] 0.77; 95% CI, 0.51–1.2; I^2=0) and progression to ESRD (6 studies, N=1,814; RR 1.1; 95% CI, 0.73–1.5; I^2=62%) in those following a low-protein diet compared with a normal protein diet. A very-low-protein diet compared with a normal protein diet was found to reduce the progression to ESRD (10 studies, N=1,010; RR 0.64; 95% CI, 0.49–0.85; I^2=56%) but not mortality (6 studies, N=681; RR 1.26; 95% CI, 0.62–2.5; I^2=0). Malnutrition in the form of protein energy wasting was no different between patients in the low-protein and very-low-protein diet groups (15 studies, N=2,373; RR 1.31; 95% CI, 0.42–4.1). There was no difference in body mass index in patients with normal and low-protein diets or low-protein and very-low-protein diets. This systemic review was limited by performance bias because of the open-label nature of the studies, as well as discrepancies between dietary adherence of the patients.

The 2020 National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) made dietary recommendations for patients with CKD stage 3 to 5.[2] A low-protein diet was defined as 0.55 to 0.60 g dietary protein/kg/day and a very-low-protein diet as 0.28 to 0.43 g dietary protein/kg/day with the addition of amino acid analogs to meet the 0.55 to 0.60 g/kg/day requirements. In metabolically stable adults without diabetes and not on dialysis, a low-protein diet or a very-low-protein diet was recommended to decrease end-stage kidney disease or death (KDOQI grade 1A—high quality of evidence) and perhaps to improve quality of life (KDOQI grade 2C—low quality of evidence). In adults with diabetes and not on dialysis, a dietary protein intake of 0.6 to 0.8 g/kg body weight per day was recommended to

maintain stable nutritional status and optimize glycemic control (committee opinion). EBP

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Nonsurgical management of carpal tunnel syndrome

EVIDENCE-BASED ANSWER

In patients with mild or moderate carpal tunnel syndrome, corticosteroid injections are slightly more effective than splinting as monotherapy for symptom relief and return of function. Combination therapy may be even more effective (SOR: B, systematic review of randomized controlled trials [RCTs] and individual RCT). Symptomatic and functional improvement is greater at six weeks with corticosteroid injections, but the data are conflicting regarding long-term benefits at three to six months (SOR: B, RCTs).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 systematic review of 28 randomized controlled trials (RCTs) compared the efficacy of multiple carpal tunnel syndrome (CTS) treatment modalities (manual therapy, electrotherapy, and pharmacology) including both splinting and corticosteroid injection.[1] Eligible studies consisted of RCTs that compared some treatment with a control, placebo, or a different treatment. Included patients had mild to severe idiopathic CTS with or without systemic pathology. Studies included validated pain and function variables, such as the Boston Carpal Tunnel Questionnaire (BCTQ-5; scale range 1–5). Six of the trials evaluated corticosteroid injections to other modalities such as other or different doses of corticosteroids, dextrose, shock wave therapy, and platelet-rich plasma. No trials evaluated corticosteroids versus splinting, but one trial evaluated corticosteroids plus splinting compared with corticosteroids alone. The data were not pooled due to heterogeneity between trials. The authors concluded that both corticosteroid injection and splinting provided significant benefit for the treatment of CTS. The trial comparing triamcinolone (with lidocaine plus splinting compared with triamcinolone with lidocaine alone found improvement in the splinting group at 12 weeks compared with injections alone (no data provided).

An open-label, parallel group, RCT evaluated methylprednisolone 20 mg injection to nocturnal splinting for six weeks in 234 patients with mild to moderate idiopathic CTS.[2] Syndrome severity was assessed using the BCTQ. All patients had symptoms for more than six weeks and were diagnosed clinically based on presenting complaint, history, and physical examination. Injections were inserted in the wrist between the proximal and distal wrist crease into the carpal tunnel space without ultrasound guidance. Corticosteroid injection was found to provide small, but significantly greater improvement than splinting in BCTQ-5 scores at the primary six-week endpoint, (mean difference [MD] –0.32; 95% CI, –0.48 to –0.16). However, by six months, there was no significant difference in BCTQ-5 scoring between groups (MD 0.06; 95% CI, –0.11 to 0.23).

A 2021 randomized controlled trial compared corticosteroids and wrist immobilization in 95 adult patients older than 40 years with CTS.[3] Patients had symptoms for at least one month and a nerve conduction study revealing moderate or severe CTS. Treatment groups received betamethasone dipropionate 1 mL (6.4 mg) with 0.5 mL 2% lidocaine (without ultrasound guidance) or bracing with a nocturnal forearm-palmar orthosis. Primary outcomes included BCTQ-5 at one week, one month, three month, and six months. Separate analysis of intervention impact was performed on the 8-point Function-Specific Scale (FSS) and 11-point Symptom-Specific Scale (SSS; both embedded in, but scored differently than the BCTQ-5). There was no significant difference in

either BCTQ score at seven days. There was a significantly lower scores in the SSS of the corticosteroid group compared with the immobilization group at one month (1.7 vs 2.2; $P<.05$), three months (1.8 vs 2.6; $P<.05$), and six months (1.8 vs 2.7; $P<.05$). There was also a significantly lower score in the FSS of the steroid group at three months (1.9 vs 2.4; $P<.05$) and six months (1.9 vs 2.6; $P<.05$). EBP

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What are the most effective breastfeeding/chestfeeding interventions that can improve breastfeeding/chestfeeding rates in healthy lactating parents and babies?

EVIDENCE-BASED ANSWER

Any form of extra chestfeeding (gender inclusive term for breastfeeding) support is associated with decreased rates of stopping chestfeeding (SOR: **B**, meta-analysis of randomized controlled trials [RCT] with high heterogeneity). Specifically, an intervention that includes chestfeeding booklets and scheduled prenatal and postpartum telephone calls with an experienced nurse have increased exclusive chestfeeding rates (SOR: **B**, RCT). At a system level, Baby-Friendly Hospital Initiative interventions increase chestfeeding rates (SOR: **B**, systematic review with moderate evidence).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2017 systematic review meta-analysis examined 73 randomized or quasi-randomized controlled trials (N=74,656 patients) examined extra lactation support versus usual care for healthy postpartum patients and their healthy term babies.[1] The trials were from 29 countries (62% of participants were from high-income countries, 34% were from middle-income countries, and 4% were from low-income countries). Interventions defined by the authors included support in the postnatal period such as reassurance, opportunities to ask questions, staff training to support patients, support groups, outreach contact to patients, and could be a single contact or multiple contacts over several months. The authors found that any form of extra support was significantly associated with a decrease in stopping any chestfeeding (partial and exclusive) before four to six weeks (33 trials, N=11,264; relative risk [RR] 0.87; 95% CI, 0.80–0.95) and before six months (51 trials, N=2,148; RR 0.91; 95% CI, 0.88–0.95). Researchers also found a decreased risk in stopping exclusive chestfeeding with any form of support (46 trials, N=18,591; RR0.88; 95% CI, 0.85–0.92). All results were determined to be moderate quality because of high heterogeneity. The authors identified factors that may have improved rates of chestfeeding including nonprofessional support (vs professional support), a face-to-face component (vs telephone), high initiation rates of chestfeeding, and a set schedule of 4 to 8 contacts, but advised caution because of the high within-group heterogeneity.

A 2019 single-center, three-arm RCT in Croatia (N=400) evaluated the effectiveness of a chestfeeding intervention on primigravidas with a singleton pregnancy who spoke Croatian and did not have any severe medical or psychiatric problems.[2] The intervention included written materials (a chestfeeding booklet and a general pregnancy booklet) and four scheduled proactive telephone calls with an experienced RN (1 prenatal and 3 postpartum at 2, 6, and 10 weeks). Two control groups were present, one was an active control which was identical to the intervention except for no chestfeeding booklet was provided and a standard care group. Patient baseline data revealed 99% had completed at least 12 years of education and 99% intended to chestfeed (exclusively or partially). The intervention group had significantly higher rates of exclusive chestfeeding compared with standard care at three months (81% vs 47%; odds ratio [OR] 4.6; 95% CI, 2.7–8.1) and at six months (64% vs 3%; OR 16; 95% CI, 9.1–27). The active control group also had significantly higher rates of exclusive chestfeeding at three months (68% vs 47%; OR 2.2; 95% CI, 1.3–3.8) and at six months (16% vs 3%; OR 2.3; 95% CI, 1.4–3.9) compared with standard care.

A 2018 systematic review by the Agency for Healthcare Research and Quality (AHRQ) included 40 studies (RCTs, systematic reviews, and observational studies with a control group) that examined the effectiveness of system-based interventions in improving chestfeeding rates.[3] They graded the strength of evidence (SOE) using the AHRQ Evidence-based Practice Center Program guidelines (a meta-analysis was not completed). The authors found that Baby-Friendly Hospital Initiative (BFHI) interventions increased chestfeeding rates through 12 months' postpartum and rated the evidence as moderate. They additionally found a number of interventions that had low-grade evidence in improving chestfeeding rates including BFHI policies that were modified and implemented into primary care, continuity of nursing care during prenatal and postpartum visits, staff education in conjunction with postpartum home visits, and WIC-based and community-based peer support programs. EBP

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Does exclusive breastfeeding versus cow's milk formula exposure or length of breastfeeding decrease the incidence of pediatric asthma or eczema?

EVIDENCE-BASED ANSWER

The diagnosis of asthma in children less than seven years old is lower in exclusively breastfed infants and in infants with greater than six months of breastfeeding compared with those less than six months of breastfeeding (SOR: **B**, meta-analysis cohort studies). Asthma is diagnosed more frequently in children breastfed along with supplementation of cow's milk formula compared with supplementation with elemental formula (SOR: **B**, randomized controlled trial). Partial and exclusive breastfeeding for at least six months is associated with a decreased risk of developing childhood eczema (SOR: **B**, cohort study).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 meta-analysis of 42 cohort studies (N=714,879) examined the association between three comparison groups of breastfeeding status (more exclusive breastfeeding vs less exclusive breastfeeding, more breastfeeding compared with less breastfeeding, and ever breastfed vs never breastfed) and the development of childhood asthma.[1] The meta-analysis included children less than 18 years old with asthma diagnosed by a physician or by symptoms meeting guideline criteria. Children in the more exclusive versus less exclusive breastfeeding group had a 19% lower risk of developing asthma (17 studies, N=30,587; odds ratio [OR] 0.81; 95% CI, 0.72–0.91). Children who were breastfed for greater than six months (which included exclusive and nonexclusive breastfeeding) as compared with less than six months demonstrated a 24% lower risk of asthma development (15 studies, N=not provided; OR 0.76; 95% CI, 0.68–0.85). Infants with any breastfeeding for greater than three months versus less than three months showed 21% less asthma diagnosis (10 studies, N=not provided; OR 0.79; 95% CI, 0.71–0.87). No difference was noted in rates of asthma between children in the ever breastfed and never breastfed groups (18 studies, N=89,861; OR 0.87; 95% CI, 0.72–1.04). In addition, more versus less breastfeeding was not associated with reduction in asthma development in children beyond seven years old (8 studies, N=not provided; OR 1.39; 95% CI, 0.9–2.2). Limitations included the lack of stratification to assess whether the incidence of asthma differed by sex.

A 2020 unmasked randomized controlled trial (n=312) examined the relationship between exposure to versus avoidance of cow's milk formula and the development of asthma or recurrent wheezing in infants at risk for atopy.[2] Increased risk was defined as at least one first-degree relative with a history of atopic disease, including asthma, atopic dermatitis, food allergy, allergic rhinitis, or hay fever. Infants were randomly assigned to breastfeeding supplemented with amino acid–based elemental formula or with cow's milk–containing formula for the first five months of life. Patients were followed up at their second birthday and assessed for the primary outcome of incidence of asthma or recurrent wheeze as diagnosed by a pediatric allergy specialist. The diagnosis of asthma or recurrent wheeze was lower in the elemental formula supplementation group (9.9%) compared with the cow's milk formula group (17.9%) (risk difference –0.079; 95% CI –0.16 to –0.002). Small sample size, subgroup analyses, and a study conducted at a single urban Japanese center may limit generalizability.

A 2016 prospective birth cohort study (n=186) examined the impact of duration of partial or exclusive breastfeeding versus formula feeding on the development of atopic disease in the children studied.[3] This study was included in the meta-analysis above but is included here separately because it explores the relationship between breastfeeding and eczema and allergic rhinitis, conditions other than asthma that are part of the atopic spectrum. The cohort consisted of children one to four years old followed in an outpatient setting in Taiwan, and 56% of patients were female, the average gestational age at birth was 38 and 1/7 weeks, and maternal age range was 26 to 36 years old at the time of birth. An asthma diagnosis was noted in 13% of parents, and an eczema diagnosis was noted in 19% of the parents. Eczema was defined as a pruritic rash affecting the face or the extremities of the children with a chronic relapsing course. Exclusive breastfeeding was defined as only breastmilk and water for feeds, and partial breastfeeding included infants who were breastfed and given formula and other complimentary foods. Breastfeeding (any type) for six months was associated with a lower risk of eczema at one year old (OR 0.23; 95% CI, 0.07–0.7) and at two years old (OR 0.36; 95% CI, 0.15–0.9). No difference was noted in eczema rates at three years old (OR 0.84; 95% CI, 0.35–2) or at four years old (OR 1.5; 95% CI, 0.58–3.6). Partial breastfeeding for less than six months compared with exclusive breastfeeding for six months or longer did show an increased risk of developing eczema at one year old (OR 4.4; 95% CI, 1.1–17) and at two years old (OR 6.6; 95% CI, 1.7–26). Similar to exclusive breastfeeding outcomes, partial breastfeeding for more than six months was associated with a decreased risk of eczema at one year old (OR 2.9; 95% CI, 0.64–13) and at two years old (OR 2.1; 95% CI, 0.46–9.5). Formula feeding was not found to be protective against eczema development at one year old (OR 0.59; 95% CI, 0.06–5.95) or at two years old (OR 2.45; 95% CI, 0.52–12). EBP

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Belly bands as treatment of low back pain in pregnancy

EVIDENCE-BASED ANSWER

Possibly. The use of maternity support garments may result in a reduction of low back pain (LBP), increased function, and increased quality of life compared with management with information about low back pain and not using any support garments (SOR: B, systematic review not limited to randomized controlled trials [RCTs]). Pregnant patients using a standard pelvic abdominal support belt and a modified vest-like lumbar pelvic belt both have significantly less LBP pregnant patients who do not wear any belts (SOR: C, small RCT).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2019 systematic review of three randomized controlled trials (RCTs), two pilot studies, and one observational study (N=386) attempted to isolate the effect of maternity support garments (MSGs) on low back and pelvic girdle pain in pregnancy.[1] Three of these studies focused specifically on MSGs effect on low back pain (LBP) in women at least 20 weeks pregnant. The results were not pooled due to study heterogeneity in design and evaluation methods. One RCT (n=105; Iran) examined the use of a nonrigid lumbopelvic belt plus information about LBP, versus an exercise program plus information, versus information alone. Pain was assessed using a visual analog pain scale (VAS, 11-point scale, 0 no pain and 10 worst pain possible), function was assessed by the Oswestry Low Back Pain Disability Index (ODI, a 10-point questionnaire assessing the impact of pain on ADLs; score range 0–50 with higher scores corresponding to increasing disability and a difference of 10 points indicating a different severity of disability), and quality of life was assessed using a modified version of the World Health Organization Quality of Life Questionnaire (WHOQOL-BREF, 26 point questionnaire addressing 4 quality of life domains: physical, psychological, social, and environmental). The support belt plus information led to a significant reduction of LBP based on the VAS score (no data provided) and of functional disability based on the ODI score (no data provided) and significant increase in quality of life scores (no data provided) based on the WHOQOL-BREF more than information alone. A second RCT (n=94; Australia) compared a group wearing a BellyBra (full torso garment with shoulder straps) versus a control group wearing a Tubigrip (tubular garment spanning from under the breasts to the pelvis), worn for an unspecified amount of time. Pain was assessed using an 11-point VAS, and quality of life was assessed using the Satisfaction with Life Scale (SWLS, 7-point scale with score range of 5–35; higher values corresponding with increased satisfaction). The BellyBra led to significant reduction in LBP compared with the Tubigrip as quantified by VAS scores while sleeping (3.4 vs 4.8; P=.007), getting up from a sitting position (4.2 vs 5.4; P=.02), and walking (3.3 vs 5.3; P=.001). Both groups had improvement in LBP with the use of MSG demonstrated by decreased VAS scores compared with the baseline (no data provided). There was no significant difference in SWLS between groups or from the baseline. Finally, a prospective cohort study (n=40; Seattle) compared a support belt binder versus no belt at all, worn during waking hours for two weeks. Pain was assessed by the pain in pregnancy profile (PIP) which measures the intensity and duration of pain related to activities of daily living in pregnancy. Wearing a support belt binder led to significantly fewer days [t(26)=3.5, P=.001] and hours of pain [t(26)=3.6, P=.001] based on PIP scores compared those without a belt. Limitations of these studies included small sample sizes making subgroup analysis by patient characteristics impossible, study heterogeneity leading to imprecision

of effect benefits, and these unblinded study designs do not rule out placebo effect.

A single-center RCT (n=48; Iran) published in 2022 examined the effect of a modified support belt (abdominal, lumbopelvic support, and shoulder straps) versus a standard belt (abdomen and pelvis support only) versus a control group (no belt use) on low back pain in pregnancy.[2] The population included patients carrying singleton pregnancy >20 weeks gestation, with moderate to severe LBP. The primary outcome was pain intensity assessment using a visual analog scale (100-point scale, 0 no pain and 100 worst pain possible) and the ODI score described above. VAS scores improved with both the modified belt (mean difference [MD] 12; 95% CI, 11–13) and the standard belt (MD 5.9; 95% CI, 4.7–7.0) compared with the control group. This was also true for ODI score improvement using the modified belt (MD 6.3; 95% CI, 5.7–7.0) and the standard belt (MD 5.1; 95% CI, 4.5–5.8) compared with control. Furthermore, the modified belt had more improvement on LBP when compared with the standard belt based on the pain VAS (MD 5.8, 95% CI, 4.5–7.1). EBP

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Does initial therapy with a GLP-1 agonist in adults diagnosed with type 2 diabetes mellitus lead to better outcomes than traditional initial therapy with metformin?

EVIDENCE-BASED ANSWER

In patients with diabetes mellitus type 2, initial therapy with a GLP-1 agonist results more patients achieving a HbA1c <6.5% by 26 weeks than initial metformin therapy (SOR: **C**, randomized control trials [RCTs] with disease-oriented outcomes). Patients being treated with GLP-1 may experience more side effects, particularly hypoglycemia (SOR: **C**, small RCT).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2014 randomized control trial (RCT; n=807) assessed the efficacy and safety of dulaglutide versus metformin.[1] Patients had a mean age of 56 years old; no other specific demographics were presented. Patients had an HbA_{1c} between 6.5% and 9.5% and managed with diet and exercise or a single oral antiglycemic medication at <50% maximum dose. In addition, patients had to be diagnosed with diabetes mellitus type 2 (DM-2) between three and five months before the study. If patients had been on thiazolidinediones or GLP-1 receptor agonists in the three months before the study or if they had ever been on chronic insulin, they were excluded. Patients were divided into three groups: weekly subcutaneous (SUBQ) dulaglutide 1.5 mg with a daily placebo pill (n=269), weekly SUBQ dulaglutide 0.75 mg and a daily placebo pill (n=270), and daily oral metformin (titrated weekly up to 2,000 mg/day over the first 4 weeks) with weekly SUBQ placebo (n=268). The trial consisted of a two-week wash-out period during which any previous oral antiglycemic medication was discontinued, treatment for 52 weeks, and a four-week safety follow-up period. The outcomes included change in HbA_{1c} (%), weight change (kg), and patients achieving an HbA1c <6.5%. At 26 weeks, compared with metformin, patients on both doses of dulaglutide had significantly greater HbA1c changes from baseline (see **TABLE**). No difference in weight loss was noted between dulaglutide 1.5 mg and metformin, but significantly less weight loss with dulaglutide 0.75 mg (see **TABLE**). Both dulaglutide groups had a significantly higher number of patients reach HbA1c <6.5% than the metformin group (see **TABLE**). No significant difference in serious adverse effects was noted in all three treatment arms and no deaths occurred. The most frequent side effects in all groups were GI events, including nausea, vomiting, and diarrhea.

A 2012 double-blinded RCT (n=820) across 22 countries assessed the efficacy and safety of exenatide compared with metformin and other diabetes medications.[2] Patients were 59% males with a mean age of 54 years old, HbA1c 8.5%, and BMI 23 to 45 kg/m^2. Patients were drug-naive with DM-2 not controlled with diet and exercise. The intervention group (n=248) received 2.0 mg SUBQ exenatide weekly and daily oral placebo for 26 weeks, whereas the control group (n=246) received oral metformin (dose titrated weekly to goal of 2,000 mg/day) and weekly SUBQ placebo for the same time frame. The outcomes were change in HbA1c and weight and patients who achieved HbA_{1c} <6.5%. At 26 weeks, no significant difference in HbA1c or weight was observed with exenatide compared with metformin, but significantly more patients in the exenatide group achieved HbA1c <6.5% compared with metformin (see **TABLE**). No major hypoglycemic episodes were observed, and serious adverse events occurred in <5.3% of patients. In the intervention group, nausea and diarrhea were the most common side effects, whereas diarrhea and headache were most common in the metformin control group. Limitations included follow-up based on study schedule, which may not reflect true practice and lack of compliance data.

A 2012 RCT (n=59) addressed the efficiency and tolerability of exenatide compared with metformin. Patients were obese with a new diabetes diagnosis, HbA1c 7%-10%, and BMI 28 to 40 kg/m^2. The intervention group (n=33, mean age of 59 years old) received SUBQ exenatide 5 μg twice daily for four weeks, followed by 10 μg twice daily for 22 weeks. The control group (n=26, mean age of 57 years old) was given metformin 500 mg twice daily for four weeks, followed by 500 mg

TABLE. HbA1c, weight, and patients who achieved <6.5% HbA1c for dulaglutide 1.5 mg and 0.75 mg and exenatide versus metformin at 26-week treatment

	2014 RCT[1]		2012 RCT[2]	2012 RCT[3]
	Dulaglutide (1.5 mg) vs metformin	Dulaglutide (0.75 mg) vs metformin	Exenatide (2 mg) vs metformin	Exenatide (10 μg) vs metformin
HbA1c change (%)[a]	–0.78 vs –0.56, *P*=.002	–0.71 vs –0.56, *P*=.02	–1.5 vs –1.5, NS	–2.1 vs –1.7, *P*=.045
Weight change (kg)	–2.3 vs –2.2, NS	–1.4 vs –2.2, *P*=.003	–2.0 vs –2.0, NS	–5.8 vs –3.8, *P*<.01
Patients at <6.5% HbA1c (%)	46 vs 30, *P*<.001	40 vs 30, *P*=.011	20 vs 14.5, *P*=.004	79 vs 73, *P*<.05

[a] Least square mean. NS=not significant.

three times a day. The outcomes included reduction in HbA1c, weight change, and percent of patients who achieved HbA1c <6.5%. A significant reduction in HbA1c and weight was observed for the exenatide group compared with the metformin group (see **TABLE**). Nausea was increased in the exenatide group compared with metformin, although this side effect tended to subside after several weeks of treatment. Hypoglycemia was also more common in those receiving exenatide, but no severe hypoglycemic events were noted in either group. This study was limited by a small sample size and single location. EBP

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