July 2024

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

July 2024
Volume 27 | Number 7

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FPIN
Family Physicians Inquiries Network

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

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Evidence-Based Practice, (ISSN: 2473-3717 [online]), is published monthly online on behalf of the Family Physicians Inquiries Network, Inc., by Wolters Kluwer Health, Inc., at 1800 Dual Highway, Suite 201, Hagerstown, MD 21740-6636. Business and production offices are located at Two Commerce Square, 2001 Market St., Philadelphia, PA 19103.

Postmaster: Send address changes to Evidence-Based Practice, PO Box 1610, Hagerstown, MD, 21741, USA.

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

STATEMENT OF PURPOSE

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

EDITORIAL POLICY

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DISCLOSURE

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.

Back, and better than ever: "Is high level (elite) activity safe in the postpartum period?"

CASE

You are seeing a 28-year-old G1P1 with no medical/psychiatric conditions in clinic on postpartum day 5 after delivery of a healthy baby boy by normal spontaneous vaginal delivery at 39 weeks and two days. Pregnancy was uncomplicated. She sustained a first-degree laceration during delivery requiring sutures for hemostasis. Today, she endorses slowed lochia, well-controlled pain, successful breastfeeding, and stable mood. Her vitals are stable. As a professional soccer player, she eagerly asks when you think she can return to an elite-level training schedule.

DOI 10.1097/EBP.0000000000002116

Bottom Line

Elite and professional female athletes are growing in number. For example, in the 2021 Olympic Games, female participation had risen to a high of 49% (n=5,386) compared with 23% (n=1,566) in 1984.[1] However, limited evidence that defines safe return to elite-level activity in the postpartum period is noted. The American College of Obstetricians and Gynecologists (ACOG) and International Olympic Committee (IOC) both came out with recommendations, even in the absence of "strong" evidence. Only a few studies address safety (defined here by incidence of injury), and even fewer randomized control trials exist to evaluate outcomes of pregnancy in elite-level athletes and return to training (RTT) postpartum (PP). Of the existing evidence, there seems to be an increased risk of various types of stress fractures when returning to high-level sport immediately. Devoid of "strong" evidence-based recommendations, the best return to RTT-PP recommendations are to maintain a careful, flexible, and individualized approach with close healthcare supervision and to emphasize a gradual increase in exercise/training over weeks beginning immediately in the PP period with pelvic floor muscle strengthening.

Evidence summary

A 2019 retrospective case–control study (n=34 elite athletes to active controls) found that 71% of athletes compared with 32% of controls returned to sport or training within the first zero to six weeks postpartum (P=.002).[2] Of the 24 sportswomen who returned in the first six weeks postpartum, four athletes (12%) experienced five stress fractures (3 sacrum, 1 tibia, and 1 fifth metatarsal), and notably, all four of these athletes were breastfeeding, and two lived with eating disorders.[2] The study is at high risk of type 2 statistical errors and given the retrospective design may contain recall bias. The authors noted that this was the first study to investigate many pregnancy-related and postpartum-related variables in athletes at a very high-performance level compared with controls.

A 2021 systematic review and meta-analysis of three studies (N=179) each with "very low" certainty evidence found no association between prepregnancy elite athletic exposure and postpartum injuries.[3] Sixteen reported injuries were sustained among 14 athletes (7 stress fractures and 9 "running injuries").[3] Of note, this systematic review does capture the same 5 stress fractures noted in the 2019 article above. All athletes who reported stress fractures in this review were breastfeeding and engaging in high impact sports.[3]

Recommendations of ACOG and IOC

In 2022, ACOG released an updated committee opinion on physical activity during and after pregnancy.[4] A total of 78 articles were cited, five relating to PP exercise and two specifically to athletes.[4] The updated manuscript stated that safe and effective exercise in pregnancy may begin after the 12th week of gestation and after delivery may be restarted gradually as soon as medically safe, with pelvic floor exercise initiation to start immediately after birth. In addition, ACOG stated that PP exercise had no negative effects on lactation but recommended feeding or expression before exercise to minimize discomfort with activity.[4]

In 2017, the International Olympic Committee (IOC) put forth a five-part evidence summary related to "exercise and pregnancy in elite athletes."[5,6] The systematic review analyzed 140 articles in part 5 ("Recommendations to Health Professionals") and 42 articles in part 3 ("Exercise in the postpartum period"). The IOC recommend: (1) an overall, low-impact and gradual reintroduction to sport with early initiation of pelvic floor muscle strengthening; (2) a stepwise approach to RTT, tiering the return to participation (rehabilitation, training at

intensity lower than before pregnancy), return to sport (reengagement with sport-specific training at lower than previous level), and return to performance (gradual return to full participation, performing at or above prepregnancy level); and (3) a careful, flexible, and individualized approach considerate of the athlete's personal performance, childbirth experience, lactation, and sport demands to support a RTT program.[5,6]

CASE CONCLUSION

For this 28-year-old G1P1 professional athlete, you recommend return to elite-level training as follows:

1. Pelvic floor muscle exercises to begin immediately under the guidance of a physical therapist.
2. Assessment of personal performance and goals, childbirth experience, lactation plan, and sport demands.
3. Gradual return to low-impact endurance activity with considerations to pain and bleeding, as tolerated.
4. Screening for disordered eating and vitamin D and calcium deficiencies.
5. Follow-up appointments for return to low-intensity sport-specific training and for return to full-intensity sport-specific training And competition.

EBP

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The authors declare no conflicts of interest.

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Very high high density lipoprotein-cholesterol associated with increased mortality in men

Liu C, Dhindsa D, Almuwaqqat Z, Sun YV, Quyyumi AA. Very high high-density lipoprotein cholesterol levels and cardiovascular mortality. *Am J Cardiol.* 2023;188:120-121. doi:10.1016/j.amjcard.2022.10.050

DOI 10.1097/EBP.0000000000002086

This 2023 prospective cohort study evaluated whether very high high density lipoprotein-cholesterol (HDL-C) (>80 mg/100 mL) was associated with increased cardiovascular and all-cause mortality in patients without known coronary artery disease. Patients enrolled in the United Kingdom Biobank between 2006 and 2010 were included for analysis. Researchers excluded patient with coronary artery disease onset before enrollment using diagnosis and procedure codes from the Hospital Episode Statistics (HES) data. From this population (n=415,416), 6.9% had an HDL-C >80 mg/100 ml (11% of women, 2% of men). A total of 15,320 all-cause deaths, of which 3,881 were cardiovascular deaths, occurred during a median follow-up of nine years. Patients with HDL-C <30 mg/100 ml had the lowest survival; however, patients with HDL>80 mg/100 mL also had higher adjusted risk for all-cause mortality (hazard ratio (HR) 1.11; 95% CI, 1.03–1.20; *P*=.005) and cardiovascular mortality (HR 1.24; 95% CI, 1.05–1.46; *P*=.01). When gender-stratified, men with HDL-C >80 mg/100 mL had an almost 2-fold higher adjusted risk of all-cause death (HR 1.79; 95% CI, 1.59–2.02; *P*<.0001) and cardiovascular mortality (HR 1.92; 95% CI, 1.52–2.42; *P*<.0001) as compared with women. When gender-stratified, HDL-C >80 mg/100 mL in women was not associated with an increased risk for all-cause (HR 0.97; 95% CI, 0.88–1.06; *P*=.50) or cardiovascular mortality (HR 1.04; 95% CI, 0.83–1.31; *P*=.70). To identify potential genetic causes for these findings, a weighted genetic risk score was assigned to a subgroup of the population. In adjusted models, the hazard ratios were unchanged. Researchers performed additional subgroup analyses to evaluate whether diabetes or alcohol use affected association. When stratified by sex, significant interaction was observed. Patients with HDL-C >80 mg/100 ml were more likely to be older, female, with lower body mass index, higher triglyceride levels, history of stroke/heart attack/diabetes/hypertension, higher total cholesterol, and greater alcohol consumption. Study limitations included the homogeneity of the cohort with primarily European ancestry and the potential for unknown and confounding variables. Positive alcohol use was defined as greater or equal to 3 times per week and did not address the quantity of alcohol used, which may have affected HDL-C levels.

Methods

This article was identified as a potential PURL through the standard systematic methodology described here. An additional literature search was conducted by searching PubMed with the terms “coronary artery disease” and “HDL-C” to find additional literature to place this research

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

Bottom Line: A very high HDL-C >80 mg/100 mL was associated with increased risk for all-cause and cardiovascular mortality in men. This adds to the mix of literature that high HDL-C is associated with increased cardiovascular and all-cause mortality. Clinicians should be cognizant of the association between high HDL-C and alcohol use and elucidate their patient’s alcohol use history as part of preventive screening. Lipid-lowering therapy is indicated if patients have an elevated atherosclerotic cardiovascular disease risk score. Currently, there are no formal recommendations for lowering HDL-C in men.

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The authors declare no conflict of interest.

Looping you in: the equivalence of torsemide and furosemide in heart failure

Mentz RJ, Anstrom KJ, Eisenstein EL, et al. Effect of Torsemide vs Furosemide After Discharge on All-Cause Mortality in Patients Hospitalized With Heart Failure: The TRANSFORM-HF Randomized Clinical Trial. JAMA. 2023; 329(3):214-223. doi:10.1001/jama.2022.23924.

DOI 10.1097/EBP.0000000000002041

This large, unblinded, randomized trial called "TRANSFORM-HF" sought to examine the hypothesis that torsemide is superior to furosemide in managing patients with heart failure. The study recruited 2,859 patients at 60 different hospitals in the United States who were hospitalized with heart failure—defined as either having a left ventricular ejection fraction ≤40% within 24 months of the hospitalization or an elevated natiuretic peptide level during the hospitalization. Patients with end-stage kidney disease requiring dialysis or a history of heart transplant or left ventricular assist device placement were excluded. Using a simple 1:1 randomization scheme, 1,431 patients were assigned to the torsemide group and 1,428 to the furosemide group during their hospitalization. The median patient age was 65 years old, and 37% were women. Race and ethnicity subgroups were prespecified and in alignment with the National Institutes of Health guidance with 58% self-identifying as White and 34% as Black. Patients were followed through telephone interviews done at 30 days, six months, and 12 months after discharge with the initial 1,500 patients also having longer-term follow-up (to assist with adequate event accrual) scheduled for 18, 24, and 30 months. The primary endpoint of all-cause mortality occurred in 373 patients (26.1%) in the torsemide group and 374 patients (26.2%) in the furosemide group. This resulted in a hazard ratio of 1.02 (95% CI, 0.89–1.18) in the intention-to-treat analysis, thereby proving nonsuperiority of torsemide. Secondary endpoints for rehospitalization through 30 days and 12 months also proved similarly insignificant. Although some crossover did take place, 90% were taking the assigned loop diuretic at hospital discharge and discontinuation of either loop diuretic occurred in <10% over the course of six months. Although the initial power calculations estimated the need for 6,000 patients to be enrolled, the trial's review board suggested stopping recruitment just shy of half of that number once the statistical analysis had already proven sufficient to answer the primary study question. When the trial was stopped, the median duration of patient follow-up was 17 months with small numbers (<5%) being lost to follow-up in each group.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching UpToDate, DynaMed, and PubMed with the terms "torsemide," "furosemide," "furosemide versus torsemide," and "loop diuretics AND heart failure" to find additional literature to place this research into the context of the 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: Although the previous literature suggested torsemide may have up to a 20% greater survival benefit when compared with furosemide in the treatment of heart failure, this large randomized trial demonstrated no such mortality advantage.

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Metformin: diabetes, weight loss, COVID?

Citation: Erickson SM, Fenno SL, Barzilai N, et al. Metformin for treatment of acute COVID-19: Systematic review of clinical trial data against SARS-CoV-2. *Diabetes Care*. 2023;46(7):1432-1442. doi:10.2337/dc22-2539

DOI 10.1097/EBP.0000000000002119

During the SARS-CoV2 (COVID-19) pandemic, multiple medications, including metformin, were evaluated for their efficacy against COVID-19. A systematic review (SR) of three randomized controlled trials analyzed the clinical effect of giving metformin to patients with acute COVID-19 infection. This systematic review used Synthesis Without Meta-Analysis (SWIM) guidelines, summary tables, and narrative synthesis to analyze the data. Across the three randomized controlled trials, a total of 1,761 adult patients were present, with 888 in the metformin group and 873 in the placebo or control group. One study had 80% of the total number of patients, and one study had only 20 patients total. The primary outcomes differed in all three trials, with no overlap in primary outcomes. The outcomes by trial included: (1) a composite outcome (including hypoxemia, emergency department (ED) visit, hospitalization, or death); (2) a stay of greater than six hours in an emergency setting or transfer to a tertiary hospital for COVID-19 within 28 days after randomization; and (3) days of hospitalization, oxygen need, and percent viral load. The three trials also differed in inclusion criteria, definition of risk of severe disease, vaccination status, and metformin dosage and formulation. The third trial, which only included 20 patients, was the only trial that showed statistically significant improvement in primary outcomes. Limitations to the systematic review listed by the authors included the small trial number and heterogeneity of the trial designs and outcomes. In addition, according to the Cochrane Risk of Bias 2, each of the trials had a high risk for bias. Despite these significant limitations, the SR used the data from the individual trials to look at the need for an ED visit and also hospitalization as outcomes in the individual trials, and calculated the number needed to treat (NNT) for these. In the first and the largest trial (n=1323), the NNT to prevent an ED visit was 69 and 60 in the intention-to-treat (ITT) and modified ITT (mITT) groups, respectively, with odds ratios (ORs) of 0.67 and 0.64. From the same trial, the NNT to prevent a hospitalization was 53 and 66, with OR of 0.44 and 0.45 in the ITT and mITT groups, respectively. In the second trial (n=418), the NNT to prevent an ED visit was 61 and 72 in the ITT and per protocol (PP) groups, with OR of 0.67 and 0.73. In this study, the NNT to prevent a hospitalization was 152 and 33 in the ITT and per-protocol groups, with respective OR of 0.94 and 0.61. These statistical findings could not be calculated in the third trial (n=20). The SR authors stated that the grade of evidence in this SR is moderate and further study is warranted.

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 Up to Date with the terms "metformin," "COVID-19" to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: This SR summarized three RCTs that addressed using metformin in the setting of COVID-19, although significant heterogeneity was noted among the studies, including different primary outcomes in all three trials. Clearly, further study is needed to answer the questions asked by this SR.

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The authors declare no conflict of interest.

Shaking up comfort: impact of a vibrating crib mattress on opioid-exposed neonates

Bloch-Salisbury E, Wilson JD, Rodriguez N, et al. Efficacy of a Vibrating Crib Mattress to Reduce Pharmacologic Treatment in Opioid-Exposed Newborns: A Randomized Clinical Trial. *JAMA Pediatr*. 2023;177(7):665-674. doi: 10.1001/jamapediatrics.2023.1077

DOI 10.1097/EBP.0000000000002129

This prospective, dual-site, nonblinded, randomized trial aimed to evaluate stochastic vibro-tactile stimulation (SVS) in improving symptoms and reducing the need for pharmacologic treatment in newborns with prenatal opioid exposure (POE). Term newborns with POE (n=208) with either confirmed toxicology testing or documented maternal exposure were enrolled, excluding those with a history of congenital abnormalities, hydrocephalus, grade 2 intracranial hemorrhage or larger, seizures unrelated to drug withdrawal, hemoglobin less than eight, invasive ventilatory support, or treatment for infections. The newborns, mostly female (55%), had a mean gestational age of 39 weeks, birth weight of 3,076 grams, and were mostly exposed to opioids used for medication assistance therapy (94% methadone and buprenorphine).

Newborns were randomized within the first 48 hours of life to SVS (n=104) using a patented vibrating crib mattress producing vibrations at 30 to 60 hertz (Cofab Design, LLC) on a three-hour on-off cycle or treatment as usual (TAU, n=104). There was some dropout of the study population (11% in SVS, 16% in TAU) mostly due to maternal transfer to an alternative facility. All newborns received standard-of-care nonpharmacologic strategies including feeding, holding, and using motorized seats while caregivers logged bedside activities to provide a record of time in the crib and symptoms. Newborns were monitored for signs of withdrawal using the modified Finnegan tool, a 21-symptom scale to assess severity of withdrawal. Those who had three consecutive scores of 8 or greater or two consecutive scores of 12 or greater were transferred to the neonatal intensive care unit (NICU) for administration of morphine treatment. For all infants managed with pharmacologic therapy, SVS was discontinued at the completion of morphine treatment.

Primary outcomes included the number of infants requiring morphine treatment, cumulative morphine dose, and the length of morphine treatment. In the nonadjusted analysis, morphine treatment was not significantly different in the two groups (TAU 35.6%, vs SVS 30.9%; *P*=.60), and there was not a difference hospital length of stay (TAU mean 5.7 days, SVS mean 5.9 days; *P*=.55). However, in a subset analysis (adjusted for site, sex, birth weight, opioid exposure, and feed type) infants who completed morphine treatment within three weeks, those receiving SVS had 3.18 fewer treatment days and 1.76 mg/kg less cumulative morphine dose than those assigned to TAU. Limitations included nonblinding and a reliance on caregiver bedside logging for reporting. Of note, one author holds the patent for the SVS device used.

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 Up to Date and Dynamed with the terms “neonatal abstinence syndrome” 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	No

Bottom line: The use of SVS as a nonpharmacologic adjunct in treatment of newborn with prenatal opiate exposure could lead to decreased use of morphine treatment, especially in the newborn treated in NICU who completed treatment within three weeks. However, this effect was not seen in the nonadjusted analysis of the complete randomized cohort in the newborn unit. Future study would be beneficial to better define use of SVS in this population.

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Cabotegravir for long-term PREP in patients assigned female at birth

Cabotegravir for the Prevention of HIV-1 in Women: Results from HPTN 084, a Phase 3, Randomized Clinical Trial

Delany-Moretlwe S, Hughes JP, Bock P, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial [published correction appears in Lancet. 2022 May 7; 399(10337):1778]. *Lancet*. 2022;399(10337):1779-1789. DOI 10.1097/EBP.0000000000002082

KEY TAKEAWAY: Compared with disoproxil and emtricitabine (TDF-FTC), cabotegravir significantly decreases HIV infection risk in patients assigned female at birth (AFAB). In addition, no significant difference was observed in the number of serious adverse events between the two medications.

STUDY DESIGN: Double-blinded, double-dummy, randomized control trial.

LEVEL OF EVIDENCE: STEP 2.

BACKGROUND: Literature has shown that oral pre-exposure prophylaxis (PREP) and long-acting intramuscular (IM) PREP with cabotegravir is effective for HIV prevention in cisgender men and transgender women. The safety and efficacy of IM PREP with cabotegravir have not been studied in cisgender women or transgender men. Long-acting PREP with cabotegravir could be beneficial to these patients because they are also at high risk of HIV infection, especially in sub-Saharan Africa, and a single IM injection every few weeks might allow for better adherence than daily pills.

PATIENTS: AFAB patients.
INTERVENTION: Cabotegravir.
CONTROL: TDF-FTC.

OUTCOME:
PRIMARY OUTCOME: HIV infection.
SECONDARY OUTCOME: Serious adverse events and injection site reaction.
METHODS BRIEF DESCRIPTION:

- Patients were AFAB with a median age of 25 years old (18-45 years old), 97% Black/African, 99% cisgender female, 20% positive for chlamydia, two episodes of receptive vaginal intercourse in the previous 30 days, HIV negative, and consented to long-acting contraception.
- Patients were blindly assigned in a 1:1 ratio.
  - The intervention group received cabotegravir 600 mg IM every eight weeks for 185 weeks.
  - The control group received TDF-FTC 300 mg to 200 mg PO and intralipid 20% fat emulsion (placebo) IM every eight weeks for 185 weeks.
- At each visit, patients were tested for pregnancy and for HIV infection.
- Safety was assessed using the number of serious adverse events (eg, hospitalization for fetal distress and respiratory tract infection, seizure) and injection site reactions.

INTERVENTION (# IN THE GROUP): 1,592
COMPARISON (# IN THE GROUP): 1,586
FOLLOW-UP PERIOD: 30 months

RESULTS:

- Primary outcome
  - Cabotegravir significantly reduced the risk of HIV infection compared with TDF-FTC (cabotegravir, 0.2 cases/100 person-years vs 1.85 cases/100 person-years; hazard ratio [HR] 0.12; 95% CI, 0.05-0.31).
- Secondary outcomes
  - No significant difference was observed in the number of serious adverse events between the two medications.
  - Injection site reaction was more common in the cabotegravir group, but it did not lead to discontinuation of the product and so was not considered a serious adverse event.

LIMITATIONS:

- Most participants were Black/African which limited generalizability. EBP

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How do vaccinations and comorbidities affect "long COVID" risk?

Risk Factors Associated With Post–COVID-19 Condition: A Systematic Review and Meta-analysis

Tsampasian V, Elghazaly H, Chattopadhyay R, et al. Risk Factors Associated With Post-Covid-19 Condition. *JAMA Int Med.* 2023;183(6):566. DOI 10.1097/EBP.0000000000002072

KEY TAKEAWAY: Demographic characteristics including sex, older age, higher BMI, and smoking as well as preexisting comorbidities including anxiety, depression, asthma, chronic obstructive pulmonary disease (COPD), diabetes, ischemic heart disease (IHD), and immunosuppression were associated with post–COVID-19 conditions (PCCs). Hospitalization for acute COVID-19 infection inferred higher PCC risk; vaccination against COVID-19 was protective against PCC.

STUDY DESIGN: Systematic review and meta-analysis of 41 observational studies (N=860,783).

LEVEL OF EVIDENCE: STEP 1.

BRIEF BACKGROUND INFO: A proportion of individuals infected with COVID-19 demonstrate persistent symptoms postinfection. Post-COVID conditions (PCCs), colloquially known as "long COVID," are defined as a group of symptoms present three months post–COVID-19 infection and lasting four or more months. Risk factors for PCCs have not been well-defined. Identification of individuals at higher risk of PCCs would allow for early and appropriate clinical support.

PATIENTS: Adults with COVID-19.
INTERVENTION: Presence of risk factor.
CONTROL: Absence of risk factor.
OUTCOME: Risk of developing PCC.

METHODS BRIEF DESCRIPTION:
- Researchers searched MEDLINE and Embase databases for studies investigating risk factors for PCC in adult patients diagnosed with COVID-19.
- Included studies used the WHO definition of PCC requiring >1 symptom for >three months post–COVID-19.
- Included studies were cohort, case-control, and cross-sectional studies that included both hospitalized and nonhospitalized patients.
- Risk factors evaluated for this meta-analysis included age, biological sex, BMI>30 kg/m2, smoking status, anxiety, depression, asthma, chronic kidney disease, COPD, diabetes, ischemic heart disease, immunosuppression, and vaccination status.
- Odds ratios for each risk factor were pooled with random-effects model.
- Publication bias was ascertained through funnel plots and Egger's test.

INTERVENTION (# IN THE GROUP): Not available.
COMPARISON (# IN THE GROUP): Not available.
FOLLOW UP PERIOD: 3 to 13 months.

RESULTS:
- Demographic factors associated with an increased risk of PCC were as follows:
  - Female sex (odds ratio [OR] 1.6; 95% CI, 1.4–1.7).
  - Age 40 years and older (OR 1.2; 95% CI, 1.1–1.3).
  - BMI>30 kg/m^2 (OR 1.2; 95% CI 1.1–1.2).
  - Currently smoking (OR 1.1; 95% CI, 1.07–1.13).
- Comorbidities associated with an increased risk of PCC were as follows:
  - Anxiety or depression (OR 1.2; 95% CI, 1.02–1.4).
  - Asthma (OR 1.2; 95% CI 1.2–1.4).
  - COPD (OR 1.4; 95% CI, 1.1–1.8).
  - Diabetes (OR 1.06; 95% CI, 1.03–1.09).
  - Immunosuppression (OR 1.5; 95% CI, 1.1–2.2).
  - Ischemic heart disease (OR 1.3; 95% CI, 1.2–1.4).
- Chronic kidney disease was not a significant risk factor for PCC.
- Patients who required hospitalization for acute COVID-19 infection demonstrated a significantly higher risk for PCC (OR 2.48; 95% CI, 1.97–3.13).
  - Those with ICU admission demonstrated a higher PCC risk (OR 2.4; 95% CI, 2.2–2.6).
- Vaccination with 2+ doses of a COVID-19 vaccine demonstrated a 40% lower risk of PCC (OR 0.57; 95% CI, 0.43–0.76).

LIMITATIONS:
- High heterogeneity among studies resulted in many of the planned analyses not being conducted.
- Potential for bias was high in many of the included studies, and publication bias was present in the studies examining BMI as a risk factor.

- Outcomes and how they were measured varied greatly across studies. EBP

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Colchicine can do more

Citation: Association of Low-Dose Colchicine With Incidence of Knee and Hip Replacements: Exploratory Analyses From a Randomized, Controlled, Double-Blind Trial

Heijman MWJ, Fiolet ATL, Mosterd A, et al. Association of Low-Dose Colchicine With Incidence of Knee and Hip Replacements: Exploratory Analyses From a Randomized, Controlled, Double-Blind Trial [published online ahead of print, 2023 May 30]. *Ann Intern Med*. 2023;10.7326/M23-0289. doi:10.7326/M23-0289. DOI 10.1097/EBP.0000000000002075

KEY TAKEAWAY: Once daily 0.5 mg of colchicine can decrease two-year total knee replacement (TKR) and total hip replacement (THR) by 31% in patients with coronary artery disease.

STUDY DESIGN: Randomized, double-blind trial.

LEVEL OF EVIDENCE: STEP 2.

BACKGROUND: Osteoarthritis (OA) is one of the leading causes of pain worldwide. Anti-inflammatory medications are widely used for pain in OA. While not labeled for treatment of OA, colchicine has anti-inflammatory effects that have short-term effects on pain for patients with OA. Colchicine has also been effective in decreasing cardiovascular events in patients with coronary artery disease.

PATIENTS: Adult patient with coronary artery disease.
INTERVENTION: 0.5 mg colchicine daily.
CONTROL: No colchicine/placebo.
OUTCOME: Reduction in TKR or THR rate.
SECONDARY OUTCOMES: outcomes by sex and stratification by history of gout.

METHODS BRIEF DESCRIPTION:
- Patients all had pre-existing coronary artery disease.
- 0.5 mg daily colchicine versus placebo followed for two years.
- Primary outcomes of TKR and THR were recorded for each group over two years.

INTERVENTION (# IN THE GROUP): 2,762
COMPARISON (# IN THE GROUP): 2,760
FOLLOW UP PERIOD: TWO YEARSt

RESULTS:
Primary outcome
- Colchicine resulted in fewer patients with TKR or THR compared with placebo (hazard ratio [HR] 0.69; 95% CI, 0.51-0.95; number needed to treat = 96).

Secondary outcomes
- No difference was observed in women between the groups (HR 1.1; 95% CI, 0.57–2.11).
- In men, colchicine resulted in a reduction in TKR/THR (HR 0.59; 95% CI, 0.41–0.85).
- Excluding patients with gout at baseline, colchicine decreased TKR and THR compared with placebo (HR 0.68; 95% CI 0.49–0.94).

LIMITATIONS:
- Different doses of colchicine were not studied.
- Patients were not screened for level of pre-existing OA.
- Very short period for the study in relation to the progression of OA.
- Unclear if this can be generalized to patients who do not have coronary artery disease.
- 134 dropped from the trial for various reasons including death and lack of follow-up EBP

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Does buprenorphine reduce mortality in adults with opioid use disorder compared with methadone?

EVIDENCE-BASED ANSWER

No difference is noted in all-cause mortality in patients with opioid use disorder undergoing methadone or buprenorphine treatment (SOR: **B**, systemic review of randomized controlled trial s and cohort studies). Buprenorphine treatment may be associated with a lower suicide mortality rate (SOR: **C**, single retrospective cohort study) compared with methadone.

DOI 10.1097/EBP.0000000000002138

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

A 2021 meta-analysis of 15 randomized controlled trials (RCTs) and 36 retrospective cohort studies (N=753,486) examined the association between all-cause and overdose-specific mortality rates in and out of treatment among patients undergoing opioid agonist treatment.[1] Patients were adults being treated with either methadone or buprenorphine in the community, hospital, or prison setting. Majority of those included were men (69%) with a mean age of 34 years old. Dosing varied between studies with mean dosing for buprenorphine at 16 mg sublingual daily and methadone at 60 mg oral daily. All-cause mortality was evaluated and compared for methadone (7 RCTs, 23 cohort studies) to buprenorphine (8 RCTs, 8 cohort studies). Follow-up periods ranged from less than six months (60% of RCTs) to one to six years (60% of cohort studies). Overall, associations for all-cause mortality were not different for methadone (23 studies, N=457,750; rate ratio [RR] 0.47; 95% CI, 0.41–0.54) versus buprenorphine (8 studies, N=168,288; RR 0.34; 95% CI, 0.26–0.45) when compared with no treatment. Total number of deaths stratified by treatment type were not reported. However, rates for all-cause mortality during the first four weeks of treatment compared with during the rest of treatment were significantly higher for methadone (RR 2.01; 95% CI, 1.55–5.09; I^2=90%) but not significant for buprenorphine. Limitations included heterogeneity in study design and lack of studies with head-to-head comparisons of all-cause mortality between methadone and buprenorphine opioid agonist therapy.

A 2022 retrospective cohort study (N=61,997) compared all-cause, suicide, and overdose mortality rates for buprenorphine and methadone therapy in patients receiving care at United States Veteran Affairs facilities.[2] Patients were majority men (93%) with a mean age of 48 years old and followed for a median of two calendar years. Calendar years for when patients did not receive opioid agonist therapy were excluded. Treatment types were extracted through prescriptions data from a medical claim database. Because of known differences in treatment by region, researchers controlled for regions by using the region where patients lived as an instrumental variable, a statistical tool to remove unmeasured bias attributed to that variable. Veteran's Administration (VA) mental healthcare consists of 115 Mental Health Referral regions (MHRRs), which were divided into three terciles of methadone use (tercile 1—4.90% received methadone; tercile 2—19.50% received methadone, tercile 3—75.10% received methadone). The results were modeled and controlled using probit regression. Outcomes were controlled for by age, gender, race and ethnicity, marital status, rurality, level of VA disability, and indices of homelessness and physical/mental health. When comparing the mean mortality rates per 10,000 calendar years between tercile 1 (least predicted methadone use) and tercile 3 (highest predicted methadone use), the probit model identified significantly lower mean rates in tercile 1 that were nearly identical to the other two models for all-cause mortality (probit model mean difference [MD] 37; 95% CI, 21–54) and suicide mortality (probit model mean difference [MD] 4.2; 95% CI, 1.8–8.3). No difference was identified for overdose mortality. Because of the population of the study consisting of only US veterans, the generalizability of the results is limited. EBP

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What is the best treatment for shin splints?

EVIDENCE-BASED ANSWER

No clearly superior treatment for medial tibial stress syndrome (MTSS or "shin splints") has been identified. Iontophoresis, phonophoresis, ice massage, ultrasound therapy, periosteal pecking, and extracorporeal shockwave therapy may be effective (SOR: **C**, systematic review of small randomized controlled trials [RCT] and cohort studies). Foot orthoses with arch support may decrease symptom severity by up to 80% (SOR: **C**, small RCT). Prolotherapy may decrease pain in refractory cases (SOR: **C**, case series).

DOI 10.1097/EBP.0000000000002065

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

A 2013 systematic review (9 RCTs, 2 cohort studies; N=579) examined the efficacy of different treatments for MTSS.[1] Patients included adults (16–56 years old) with MTSS, defined as diffuse, exercise-induced pain on the medial border of the tibia. The interventions evaluated included iontophoresis (transdermal drug delivery using a weak electrical current), phonophoresis (transdermal drug delivery using sound waves), ultrasound, low energy laser, periosteal needling, compression stockings, lower leg bracing, pulsed electromagnetic field, radial extracorporeal shockwave therapy (ESWT, shockwaves generated using compressed air and a projectile through a tube), and focused ESWT (more focused shockwaves using a lens). In addition, RCTs evaluating lower leg bracing versus no bracing, and iontophoresis versus phonophoresis were pooled using a fixed effects model. Outcomes were varied and included perceived pain and degree of or time to recovery. Of the treatments studied, iontophoresis, phonophoresis, ice massage, ultrasound therapy, periosteal needling, and ESWT showed significant difference in outcomes measured compared with controls, though with limited quality evidence (**TABLE 1**). Stretching and strengthening exercises were not effective in treating MTSS. Limitations included variability in study quality, patient population, comparison treatments, and the diversity of outcomes measures making comparison and pooling of data difficult. All included studies were small and found to have significant methodological bias concern.

A 2022 RCT (n=50) evaluated the use of arch-support foot-orthoses (ASFO) for the treatment of MTSS.[2] The study population included female patients, 18 to 25 years old, with a diagnosis of MTSS and low arches. Researchers excluded patients who had used foot orthoses or participated in physical therapy in the prior six months or had surgery or traumatic injury in the past year. The intervention was bilateral ASFO used in conjunction with a multimodal treatment program (ice massage, ankle muscle exercises, and ESWT). The comparison was bilateral sham flat noncontoured orthoses (SFO) used with the same multimodal treatment program. Primary outcomes included MTSS severity using a symptom scale, assessed at baseline and weeks 6, 12, and 18. Patients in the ASFO arm reported a 33% reduction in symptom severity from baseline at 6 weeks and a 50% reduction at 12 weeks, compared with a 16% and 40% reduction at the same intervals for those in the SFO arm ($P<.05$). By week 18, however, no difference was observed in outcomes between groups, with both reporting greater than 70% reduction in symptom severity. Study validity was affected by small sample size and patient demographics which limit generalizability.

A 2021 case series (n=18) evaluated ultrasound-guided prolotherapy for treatment of recalcitrant MTSS.[3] Researchers included adults (83% male; mean age 31 years old) who had failed conservative management based on history, examination, and MRI showing persistent periosteal or bone marrow edema. Approximately 1 mL aliquots of a 15% dextrose solution were injected along the length of the area of maximal pain. Patients were also treated with ice and compression stockings and advised to take three days of relative rest followed by a graded return to activity program. Primary outcomes were pain (assessed by visual analog scale), degree of recovery (measured by Likert scale), and return to sport, measured at 1, 2, 4, 18, and 52 weeks of follow-up. Pain scores decreased for 89% of patients at four weeks ($P<.001$) and 18 weeks ($P<.001$), with a 60% median improvement from baseline, although

TABLE 1. Studies with significant findings evaluating treatment modalities for medial tibial stress syndrome (MTSS)[1]

Study design	Treatment(s) studied	Population	Intervention/comparison	Primary outcomes	Results
RCT	Iontophoresis, ice massage, phonophoresis, and ultrasound versus control	n=50 Age: 18–25 y Sex ratio: unreported	Group 1: Iontophoresis Group 2: Ice massage Group 3: Ultrasound and phonophoresis Group 4: Ultrasound Group 5: Control (no treatment)	Change in perceived pain (1–10 scale) pretreatment/post-treatment	(Mean) Group 1: 5.0 Group 2: 5.6 Group 3: 5.2 Group 4: 4.8 Group 5 (control): −1.9 $P<.01$ (Groups 1–4 vs 5) No significant difference between Groups 1–4
RCT	Periosteal needling+ultrasound vs ultrasound	n=44 Age: 20–52 y Sex ratio: 73% M 27% F	Group 1: Periosteal needling and ultrasound therapy Group 2: Ultrasound therapy	Pain and disability index (0–50 scale) obtained before treatment 4	Mean Group 1: 18 Group 2: 25 $P=.02$
Non RCT	Radial extracorporeal shockwave therapy (ESWT)	n=94 Age: 18–56 y Sex ratio: 43% M 57% F	Group 1: Home exercise program+radial ESWT Group 2: Home exercise program alone	Degree of recovery after four months (6-point Likert scale)	Success rates Group 1: 64% Group 2: 30% $P<.001$
Non RCT	Focused extracorporeal shockwave therapy (ESWT)	n=42 Age: 16–43 y Sex ratio: 35% M 65% F	Group 1: Running program alone Group 2: 6 Running program+focused ESWT	Days from inclusion to completing running program	Mean Group 1: 92 Group 2: 60 $P=.008$

a wider range of pain scores were seen at longer-term follow-up. At 52 weeks, 33% of patients rated their MTSS as "completely recovered" or "much improved" and 22% of patients had returned to sport at preinjury levels. The study design, which lacked a comparison group, makes drawing cause-effect conclusions impossible and limits generalizability. EBP

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

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What is the risk of asthma exacerbation for pregnant patients with a history of asthma who are put on labetalol for hypertension?

EVIDENCE-BASED ANSWER

There may be an increased risk of asthma exacerbation when labetalol is used to treat hypertension in pregnant patients with a history of asthma (SOR: **C**, 1 cohort study and 1 case report). Compared with other antihypertensives, labetalol increases the risk of status asthmaticus in this population (SOR: **C**, 1 cohort study). Guidelines recommend avoiding the use of labetalol because of the risk of causing bronchospasm (SOR: **C**, 1 practice bulletin and 1 guideline).

DOI 10.1097/EBP.0000000000002113

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

A 2018 retrospective cohort study (n=5,691,178) evaluated the use of intravenous (IV) labetalol (dosage information not provided) in comparison with other antihypertensive medications (ie, nifedipine and hydralazine) during delivery hospitalization.[1] Of the 5,691,178 patients, 12,486 had a diagnosis of preeclampsia and a diagnosis of asthma. Patients were 15 to 54 years old (46% were 25–34 years old), with 48% White and 28% Black. The primary outcomes included the development of status asthmaticus as determined by International Classification of Diseases-9 code. Intravenous labetalol significantly increased the risk of status asthmaticus compared with other antihypertensives (6.5 vs 1.7 per 1,000 deliveries respectively, $P<.010$; number needed to harm [NNH] =200). Study limitations included lack of data on the number of doses of IV labetalol each patient received, lack of information on patients' asthma severity, and asthma symptom control before delivery hospitalization.

A 2018 case report described a 33-year-old pregnant patient with a history of mild intermittent asthma who presented at 37 weeks and four days of gestational age with preeclampsia.[3] During her hospitalization, she received one dose of IV labetalol 20 mg for a blood pressure of >170/120 mmHg. Eleven minutes after, the patient became unresponsive and cyanotic leading to a maternal code, intubation, and emergency cesarean delivery. The patient was difficult to ventilate, likely because of bronchospasm. She had return of circulation but remained intubated and was ultimately declared brain dead on postoperative day 10 from anoxic brain injury. An autopsy found chronic lung changes that were consistent with severe asthma. The authors recommended that labetalol not be given to any patients with asthma.

A 2019 Practice Bulletin by the American College of Obstetrics and Gynecology analyzed the literature to determine best practices for treating chronic hypertension in pregnancy.[2] For both treatment of chronic hypertension and hypertensive emergencies, labetalol was listed as one of the first-choice drugs. However, the bulletin stated that both oral and IV labetalol should be avoided in pregnant patients with preexisting asthma because of the risk of precipitating bronchospasm.

A 2008 American Heart Association guideline on the use of antihypertensives in pregnancy specifically noted preexisting asthma as a contraindication to labetalol use for treatment of hypertensive emergencies in pregnancy.[4] EBP

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In a resource-limited setting, what interventions most greatly decrease unplanned pregnancies?

EVIDENCE-BASED ANSWER

In low- or middle-income countries, education on sexual health and contraception with or without provision of some form of contraceptive improves overall contraceptive use, but not unintended pregnancies (SOR: **A**, systematic review). In women with unintended pregnancies in 36 low- and middle-income countries, the most common reason for discontinuing modern forms of contraception was concerns about health or side effects (SOR: **B**, cross sectional cohort).

DOI 10.1097/EBP.0000000000002110

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

A 2021 systematic review and meta-analysis of 26 studies analyzed preconception care interventions and their effect on unintended pregnancy, initiation of sexual intercourse, and use of birth control.[1] Fourteen studies were randomized control trials and 12 were quasiexperimental. Each study focused on maternal outcomes including unintended pregnancy. Patients were women of childbearing age from low-income, lower middle-income, or upper middle-income countries. Population sizes ranged from 366 to 19,289 patients. The most common interventions included education on sexual health alone, education on sexual health combined with other strategies, and provision of contraceptives. Other interventions are summarized in **TABLE 1**. The comparison in most studies (N=25) was no intervention. A random effects model was used to conduct meta-analyses. Education on sexual health and contraception without provision of contraception did not delay initiation of sexual activity. Education on sexual health and contraception was shown to have little or no effect on the risk of unintended pregnancy (relative risk [RR] 0.42; 95% CI, 0.07–3.26). However, education on both contraception and sexual health—with or without the provision of contraception—did improve contraceptive use (RR 2.45; 95% CI 1.19–5.06). Limitations for this review included the inability to blind interventions, significant attrition, selection bias, and overall low-quality evidence. Although there was statistical significance in improving contraceptive use with education, the clinical significance on preventing unplanned pregnancies was unclear.

A 2020 cross sectional study used contraceptive calendar data from Demographic and Health Surveys in low- and middle-income countries to analyze why women with unintended pregnancies discontinued their last contraceptive method.[2] The questionnaire was administered to women 15 to 49 years old and included contraceptive history over the previous five calendar years. The data sets comprised surveys from 2005 to 2014 from 36 countries. The last method of contraceptive was defined as no contraception, traditional method of contraception (withdrawal, periodic abstinence, and calendar rhythm method), short-acting modern methods of contraception (pills, injections, barrier methods, lactational amenorrhea), and long-acting methods of contraception (intrauterine device, implant, male/female sterilization). Prevalence of use of contraception by type of method with all unintended pregnancies was calculated for individual countries and the global data set. Cross-tabulations were conducted and then stratified by residence, education, and wealth. Overall, 56.3% of women with unintended pregnancy had not used contraception in previous five years. The primary reason for discontinuing traditional methods was failure (becoming pregnant, 83.8%), then inconvenience (5.2%). In short-acting modern contraceptives, 41.3% were discontinued because of side effects and health concerns and 25.1% because of failure. Of women using long-acting modern methods, 40.2% discontinued because of side effects and health concerns, 22.5% from failure, and 14.8% because of cost. Most women with

TABLE 1. Number of studies per chosen intervention[1]	
16	Education on sexual health alone
6	Education on sexual health combined with other strategies
3	Provision of contraceptives
2	Cash transfers
1	Peer referrals to healthcare providers and training of healthcare providers
1	Training of health workers and peer condom marketing
1	Referrals, family members education, and improvement of contraceptive services
1	Skills training, referrals to microsaving sand credit groups, and training of healthcare providers
1	Development of youth partnership groups and education subsidies

unplanned pregnancy had not recently used contraception, and an additional 9.9% used traditional methods with high rates of failure. The limitations of this study included recall bias inherent to retrospective surveys, underreporting, limited choices for responses, and not accounting for improper use of contraceptive methods. EBP

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

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Does OMT reduce symptoms of obstructive pulmonary disorders?

EVIDENCE-BASED ANSWER

Patients with COPD may have greater improvement in the 6-Minute Walk Test (6MWT) and residual lung volume with OMT plus pulmonary rehab than with sham manipulation and pulmonary rehab (SOR: **C**, small RCT). Patients with COPD receiving spinal manipulation, exercise, and soft tissue therapy appear to have greater improvement in the 6MWT and FVC than withspinal manipulation alone (SOR: **C**, small RCT).

DOI 10.1097/EBP.0000000000002054

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

A small 2012 randomized controlled trial (RCT; n=20) examined the effectiveness of osteopathic manipulative treatment (OMT) compared with soft (sham) manipulation in the treatment of COPD.[1] Patients were adults recruited from a pool of COPD patients repeatedly admitted to the Operative unit and Respiratory rehabilitation unit in Milan from January to May 2008. Mean age was 64 years old and

mean FEV_1 was 26.9% of predicted. Selected patients had stable stage 3 COPD, with no exacerbations in the past three months. The intervention group received pulmonary rehabilitation and OMT, whereas the control group received pulmonary rehabilitation and soft manipulation (sham). The treatment period was four weeks long. The primary outcome was the 6MWT per American Thoracic Society guidelines, and secondary outcome was pulmonary function test assessed by spirometry. Patients in the intervention group did better on the 6MWT compared with the control group (mean difference [MD] 48.8 m; 95% CI, 17–80.6; $P=.04$). A decrease in residual volume was noted for the intervention group compared with the control group (MD –0.44 L; 95% CI, –0.26 to –0.62; $P=.001$). No reported adverse events or side effects were noted, and both pulmonary rehabilitation and OMT were well tolerated. The study was limited by small sample size and the authors' unfamiliarity with OMT.

A 2013 RCT of patients (n=15) between 45 and 60 years old examined the effect of manual therapies and exercise on COPD symptoms compared with soft tissue therapy alone.[2] Patients were volunteers 45 to 60 years old, recruited from the general population, who had been diagnosed by a respiratory specialist with moderate COPD. They were required to have the ability to ambulate unassisted and have no contraindications to spinal manipulation (SM). The intervention groups consisted of those who received soft tissue (ST) therapy consisting of gentle massage (effleurage, friction, and cross friction) to the muscles of the posterior chest wall. An ST and SM group in addition received high-velocity low-amplitude joint manipulation of the thoracic intervertebral, costovertebral, and costotransverse joints. An SM, ST, and exercise (Ex) group in addition received a regimented six-minute walking program on a leveled surface in addition to previous interventions. Therapy was offered in eight sessions over four weeks. The primary outcome was increase in forced vital capacity (FVC), forced expiratory value over 1 second (FEV_1), 6MWT, and Chronic Respiratory Questionnaire (CRQ-SAS) score within the SM and ST and SM, ST, and Ex groups compared with the ST-only group. The CRQ-SAS assesses 4 domains of symptoms with an improvement of 0.5 being clinically significant. Regarding the 6MWT, authors stated an increase in 35 m distance or 10% of baseline represented a clinically significant change. When compared with ST alone, a significant increase was noted in performance for the triple therapy group and double therapy group in distance walked (168 and 120 m, respectively) and CRQ-SAS dyspnea domain score (0.44 and 0.64, respectively). FVC significantly improved in the triple therapy group compared with the ST and triple therapy group compared with double therapy group. No major or moderate adverse events were reported after the interventions. This trial was limited by the low patient volume and subsequent lack of power to make a definitive conclusion.

In 2012, a systematic review of five RCTs and two pre–post studies (N=121), examined the use of manipulation interventions targeted at the musculoskeletal system as a management approach for COPD patients.[3] The review included studies of adults with a history of chronic obstructive airway disease (including COPD, emphysema, and chronic bronchitis) with no age restrictions. The study populations received interventions with a form of manual therapy, defined as a "clinical approach utilizing skilled, specific hands-on techniques, including but not limited to manipulation/mobilization …." Studies where manipulation therapy was included as a part of pulmonary rehab or involved techniques delivered through hand contact were excluded. Outcome measures included lung function parameter (ie, FEV_1, FVC, and VC) and patient-reported measures (ie, breathlessness). From the seven studies, little evidence was noted to support or refute the use of manipulation therapy interventions in the management of COPD. Results were limited secondary to multiple factors contributing to poor reporting and conduct of the studies; six studies were classified as having high risk of bias, three RCTs had incorrect analysis, and the studies were small (largest study with N of 35) and contained heterogeneous populations. EBP

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In adults with fibromyalgia, does cannabis compared with placebo result in pain reduction?

EVIDENCE-BASED ANSWER

A weak association with medical cannabis use and the reduction of fibromyalgia symptoms and pain is noted (SOR: **C**, systematic review of low-quality randomized controlled trials and retrospective cohorts and a retrospective case series).

DOI 10.1097/EBP.0000000000001988

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

A 2021 systematic review of 22 various studies (N=1,326) analyzed the role of the cannabinoid system in fibromyalgia (FM) syndrome.[1] Patients included were adults with existing FM diagnosed by the 2010 American College of Rheumatology guidelines. A subset of six low-quality clinical studies was identified and is summarized below. A small 2020 randomized controlled trial (RCT; n=17) measured the impact of THC-rich cannabis oil (24.44 mg/mL of THC and 0.51 mg/mL of CBD) in women over an eight-week period. After eight weeks, the THC group had a significant decrease in Fibromyalgia Impact Questionnaire (range 0–100, with lower values indicating better pain outcomes) scores compared with placebo group (30 vs 61, $P<.01$). Another small RCT from 2018 (n=20) examined treatment with inhaled Bedrocan (high THC content), Bedrolite (high CBD content), and Bediol (high CBD/high THC content) versus inhaled placebo in modulating pain threshold in women. Bedrocan and Bediol (high THC content interventions) significantly increased pressure-pain threshold compared with placebo, respectively, withstanding 7 kg ($P=.01$) and 11 kg ($P=.001$) versus 3 kg of force, but they had insignificant effect on electrical pain or spontaneous pain. Third, a 2019 prospective observational study (n=367) followed patients who were administered medical cannabis (oil, extract, flower capsules, or cigarettes). After six months of use, pain intensity (0–10 scale) was reduced significantly compared with baseline readings (median 9.0 vs 5.0, $P<.01$). Of the three remaining studies, two studies showed significant pain reduction with medical cannabis use and one study showed improvement in FM impact scores but worsening fatigue with medical cannabis. All studies reported various side effects, including dizziness, dry mouth, gastrointestinal symptoms, restlessness, and mental confusion. Of these six low-quality studies, five (83%) showed a significant improvement in FM pain or impact. Cannabis medications and their dosages were not standardized.

A 2018 retrospective case series (n=26) examined the effectiveness of medical cannabis on patients with FM.[2] Participants were adults (mean age 38 years old) who were majority female (73%), and whose data were obtained by chart review from two Israeli hospitals. Patients with malignancy-associated or rheumatic disease-associated FM were excluded. Mean duration of FM symptoms was 7.6 years, mean dose of medical cannabis used by the patients was 26 g/month, and mean duration of medical cannabis use was about 10 months. All patients smoked or inhaled medical cannabis. Symptoms were measured using the Revised Impact Questionnaire (FIQR) that measures parameters like ability to complete activities of daily living, pain, sleep, etc. The total score is measured out of 210, with lower scores indicating better outcomes. The questionnaire was completed at baseline and again after two months of treatment with medical cannabis. All patients reported significant improvement in every parameter of the FIQR, with overall scores being significantly lower posttreatment compared with baseline (77 vs 177, $P=.001$). Scores were completed within three months of starting medical cannabis treatment, and 50% of patients stopped taking any other medications for FM within two months of starting treatment. Major limitations included recall bias and the short follow-up period. EBP

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For women with medically managed abortion, what is the relative efficacy and safety of combined mifepristone/misoprostol compared with misoprostol alone?

EVIDENCE-BASED ANSWER

For medically managed abortions and miscarriages 12 to 28 weeks of gestation, combination mifepristone-misoprostol regimens have lower rates of ongoing pregnancy at 24 and 48 hours, and higher rates of complete abortion at 24 and 48 hours when compared with misoprostol alone (SOR: A, meta-analysis of randomized controlled trials [RCTs]). For medically managed abortions between 5 and 12 weeks of gestation, the combination of mifepristone plus misoprostol is more effective for complete abortion within 24 to 96 hours than the use of misoprostol alone (SOR: B, single RCT).

DOI 10.1097/EBP.0000000000002125

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

In 2020, a meta-analysis of 43 randomized controlled trials (N=8,284) compared the efficacy and safety of mifepristone-misoprostol combination to misoprostol alone for medical management of abortion at and above 12 weeks of gestational age.[1] The analysis included trials reporting a mean gestational age range of 12 to 28 weeks. Studies were excluded in which patients had spontaneous fetal demise, spontaneous abortion (incomplete, threatened, or missed), septic abortion, or preinduction mechanical cervical preparation. Patients in the combination group received 200 mg oral mifepristone followed 12 to 48 hours later by one dose of misoprostol ranging from 400 mcg to 600 mcg given sublingual, buccal, or vaginal. This was followed by additional doses of misoprostol every three to six hours up to 5 doses until termination of the pregnancy occurred. Patients in the misoprostol alone group received either placebo followed by misoprostol administration or misoprostol administration alone. Efficacy, the primary outcome, was defined as ongoing pregnancy at 24 to 48 hours postmedication administration. Safety, the secondary outcome, was defined under serious adverse events and side effects such as bleeding, pain, vomiting, diarrhea, hospitalization post-abortion, blood transfusion, need for post evacuation surgery, and death. The mifepristone-misoprostol combination compared with misoprostol alone had lower rates of ongoing pregnancy at 24 hours (5 trials, N=783; risk ratio [RR] 0.12; 95% CI, 0.04–0.35; I^2=37%) and 48 hours (4 trials, N=366; RR 0.22; 95% CI, 0.08–0.60; I^2=0%). Combination methods also had higher rates of complete abortion at 24 hours (number of patients/trials not reported; RR 1.4; 95% CI, 1.01–2) and 48 hours (number of patients/trials not reported; RR 1.1; 95% CI, 1.01–1.3). Owing to the limited number of serious adverse events, safety was not statistically evaluated. The evidence was given a rating of moderate certainty (scale of high, moderate, low, and very low certainty) except for the RR of ongoing pregnancy at 48 hours after combination regimen administration which was of low certainty evidence.

In 2018, a randomized-controlled trial (n=300) compared the efficacy and safety of oral mifepristone plus vaginal misoprostol versus vaginal misoprostol alone for management of early pregnancy loss.[2] The study included healthy women 18 years old and older (mean age 30 years) with confirmed, nonviable intrauterine pregnancy of 5 and 12 weeks of gestation. Ethnicities included 44% Black, 36% White, and 25% Hispanic. Most patients had parity greater than or equal to one (58–66%). Researchers excluded women who were noted to have incomplete or inevitable abortion, ectopic pregnancies, hemoglobin levels lower than 9.5 g/dL, clotting disorders, or currently receiving anticoagulation. Patients were randomly assigned to pretreatment of 200 mg oral mifepristone, followed by self-administration of 800 mcg vaginal misoprostol after 24 hours or self-administration of 800 mcg vaginal misoprostol alone. Initial follow-up occurred within 24 to 96 hours after administration

of misoprostol. Women without successful expulsion at follow-up were offered a second dose of misoprostol, expectant, or surgical management. All patients received a telephone call at 30 days. The primary outcome was treatment success defined as expulsion of gestational sac by the initial follow-up visit and no additional medical interventions required within 30 days. The secondary outcomes were adverse effects of medication and satisfaction/acceptability of treatment. Women in the mifepristone plus misoprostol group had higher rates of treatment success at initial follow-up than women in the misoprostol alone group (84% vs 67%; RR 1.3; 95% CI 1.1–1.4). Both groups indicated similar side effects including bleeding intensity, pain, and overall satisfaction (good, neutral) with the medical management. EBP

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In adults with chronic migraine, is neuromodulatory therapy effective for reducing migraine frequency and severity of pain?

EVIDENCE-BASED ANSWER

Overall in adults with chronic migraine, neuromodulatory therapy, in the form of transcranial magnetic and electric stimulation, can result in up to eight fewer days of migraine symptoms per month, although evidence is inconsistent with regard to a reduction in symptom severity (SOR: **B**, meta-analysis of randomized controlled trials [RCTs]). Neuromodulation of the left dorsolateral prefrontal cortex does not result in decreased pain severity but does decrease migraine frequency by 1.6 days per month (SOR: **A**, meta-analysis of RCTs).

DOI 10.1097/EBP.0000000000002124

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

A 2022 network meta-analysis of 19 randomized controlled trials (RCTs; N=1,493) evaluated the effectiveness of noninvasive brain and nerve stimulation for migraine treatment.[1] Patients had a mean age of 38 years old, 82% female, and a diagnosis of chronic, episodic, or mixed chronic/episodic migraines. The mean follow-up duration was 11.4 weeks. Patients were treated with noninvasive brain and nerve stimulation, most notably transcranial direct stimulation (tDCS) or high-frequency repetitive transcranial magnetic stimulation (rTMS) over various brain regions, although other stimulation devices were also used. Among the 19 trials, 88 patients received the tDCS intervention and 216 patients received the rTMS intervention. Seventeen trials used a sham neurostimulator device as a control with a total of 228 of patients receiving the sham device; two trials did not use controls. The primary outcomes were changes in monthly migraine days and response rate, with a successful response reported as a greater than 50% reduction in migraine frequency or days with pain. Migraine pain severity was reported as a standardized mean difference (SMD) after pooling various pain scales across trials. Secondary outcomes included posttreatment migraine pain severity and changes in rescue migraine pharmacotherapy use. The tDCS over the sensory cortex CP4+ (mean difference [MD] –8.7 days; 95% CI, –15.4 to –2.1 days), rTMS over primary motor cortex C3 (MD –8.7 days; 95% CI, –14.5 to

–3.0 days), and rTMS over left dorsolateral prefrontal cortex F3 (MD –6.3 days; 95% CI, –11.5 to –1.0 days) resulted in fewer monthly migraine days than sham/control group. In one trial (n=45), the tDCS-CP4+ intervention yielded a significant decrease in pain severity (SMD –4.1; 95% CI, –5.3 to –3.0) compared with sham. No changes were noted in the frequency of rescue medication use among intervention and control groups. The main limitations of the study were small sample sizes in some trials and a relatively short mean follow-up period.

A 2022 meta-analysis of eight RCTs (N=434) evaluated the efficacy of rTMS on analgesia and migraine frequency reduction in adults and adolescents with chronic migraine.[2] Patients (mean age 36 years old) had a diagnosis of chronic migraine with or without aura, were above 15 years old, and 80% female. Patients were treated with rTMS or sham stimulation and had an average follow-up period of one month. Patients assigned to rTMS received transcranial magnetic stimulation over the left dorsolateral prefrontal cortex (LDLPFC) or the primary motor cortex (M1). The sham used a stimulator that produced no magnetic field. Researchers characterized pain intensity using VAS or numerical pain rating scale before and after rTMS, and number of migraine attacks per month. Data were then pooled and converted to a SMD to account for the difference in standard deviation among studies. No significant decrease was noted in pain intensity between the rTMS and sham control group for LDLPFC (6 trials, N=139; SMD –0.55; 95% CI, –1.42 to 0.33) or primary motor cortex (6 trials, N=113; SMD 0.02; 95% CI, –0.63 to 0.67). After pooling all eight trials, a significant decrease was noted in migraine frequency in days per month after rTMS (SMD –1.31 days; 95% CI, –1.69 to –0.58 days; I^2=83%). Subgroup analysis of locations further showed that LDLPFC was an effective location to reduce migraine frequency (SMD –1.13 days; 95% CI, –1.62 to –0.64 days; I^2=62%), but the results for M1 were not statistically significant. Of the eight trials, four reported no adverse effects, three reported mild adverse effects such as sleepiness or dizziness, and one reported an increase in migraine pain during treatment at M1. The studies were limited by small sample sizes, a short follow-up duration of one month, and lack of real-world studies. EBP

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Does tai chi improve insomnia in older adults compared with no intervention?

EVIDENCE-BASED ANSWER

There is small, but not clinically meaningful improvement in sleep quality with tai chi when compared with usual care, nonphysical activity, routine activities, health education, low-impact exercise, or usual rehabilitative care (SOR: A, consistent data from 2 meta-analyses of randomized controlled trials [RCTs]). Tai chi may improve sleep quality compared with sleep hygiene (SOR: C, single RCT).

DOI 10.1097/EBP.0000000000002123

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

A 2022 network meta-analysis of 35 randomized controlled trials (RCTs) (N=3,519) assessed efficacy of exercise regimens for sleep quality in older adults.[1] The analysis included seven RCTs (N=653) comparing tai chi with usual care or sleep hygiene. All patients (mean age of 71 years old and 64% female) had known significant sleep disturbance based on Pittsburgh Sleep Quality Index

(PSQI) scores or Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Study interventions included tai chi, most commonly for 60 minutes duration, one to three times per week, for 8 to 24 weeks, compared with usual care or nonpharmacological interventions. Concomitant hypnotics were allowed in 1 study and not reported in all other studies. The primary endpoint was sleep quality measured by the PSQI (with scores ranging from 0 for best sleep quality to 21 for worst sleep quality); the secondary endpoint was adverse events. Tai chi improved sleep quality compared with usual treatment (6 trials, N=580; standard mean difference [SMD] –0.89; 95% CI, –1.3 to –0.44; heterogeneity not reported), although authors noted the magnitude of effect may not be clinically meaningful. Tai chi improved sleep quality by a large degree compared with sleep hygiene (1 trial, n=73; SMD –2.3; 95% CI, –3.2 to –1.4). No adverse events were reported. This analysis was limited by clinical heterogeneity in tai chi session frequency and duration among studies, lack of blinding to the intervention, and inadequate reporting of certain participant baseline characteristics such as tai chi skill level and concomitant use of pharmacotherapy.

A 2021 systematic review and meta-analysis of 22 RCTs (N=1,747) assessed efficacy of traditional Chinese exercises and general aerobic exercises for treatment of sleep disorders in older adults.[2] Eleven studies overlap with the prior meta-analysis. Ten studies included tai chi for 25 to 60 minutes duration one to four times per week for 12 to 24 weeks compared with nonphysical activity, routine activities, health education, low-impact exercise, or usual rehabilitative care. Patients had a mean age of 70 years old and 56% female predominance. One study allowed for concomitant qi gong in both the intervention and control groups. The primary endpoint was sleep quality measured by the PSQI (minimal clinically important difference 3–4). Compared with the control intervention, tai chi improved sleep quality (10 trials, N=702; weighted mean difference –1.4; 95% CI, –2.1 to –0.80; moderate heterogeneity I^2=68%), although this small change is likely not clinically meaningful. Adverse events were not reported. Patients in the control group may have received psychotropic pharmacotherapy, low-impact exercise, or educational interventions that might have lessened the relative efficacy of tai chi. This analysis was limited by clinical heterogeneity in tai chi session frequency and duration among studies, lack of blinding to the intervention, and inadequate reporting of certain patient baseline characteristics such as tai chi skill level and concomitant use of pharmacotherapy. EBP

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At what concentration does HDL-C no longer confer mortality benefit in men and women?

EVIDENCE-BASED ANSWER

Patients *with* known cardiovascular (CV) disease are at increased risk of all-cause and CV death with HDL-C >80 mg/dL (SOR: **B**, cohort study). HDL-C >80 mg/dL is associated with increased all-cause and CV death in men with and *without* coronary artery disease but not in women (SOR: **B**, cohort study). HDL-C >70 mg/dL is associated with increase in non-CV and noncancer deaths in men, whereas >90 mg/dL is associated with similar risks in women (SOR: **B**, cohort study).

DOI 10.1097/EBP.0000000000002133

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

A 2022 prospective, multicenter, cohort study conducted from 2006 to 2020 in the United Kingdom and

from 2003 to 2020 in Atlanta, GA analyzed the association between HDL-C levels and all-cause and cardiovascular (CV) death in 19,945 adult patients with coronary artery disease (CAD).[1] The study included 14,478 patients 40 to 72 years old from the United Kingdom Biobank (UKB) and 5,467 patients 18 years old or older from the Emory Cardiovascular Biobank (EmCAB). UKB patients averaged 62 years old, 76% men, and 93% White with a median follow-up of nine years. EmCAB patients averaged 63 years old, 66% men, and 73% White with a median follow-up of 6.7 years. In the UKB group, HDL-C levels >80 mg/dL were associated with increased risk of all-cause mortality (hazard ratio [HR] 2; 95% CI, 1.4–2.7) and CV death (HR 1.7; CI, 1.1–2.7). The association with all-cause mortality was also seen in the EmCAB group (HR 1.6; CI, 1.1–2.4) but not CV mortality. Subgroup analysis of UKB by gender showed that men with HDL-C >80 mg/dL were at increased risk of all-cause (HR 2.6; CI, 1.8–4) and CV mortality (HR 2.5; CI, 1.5–4.3) but not women. Of note, subjective alcohol consumption differed between men and women, introducing a possible confounding variable, because increased alcohol consumption has been linked with elevated HDL-C levels in other studies.

A 2021 prospective observational cohort study used data from 415,416 patients without CAD enrolled in the UKB to determine the association between HDL-C levels and all-cause death and CV death among men and women.[2] The study enrolled patients 37 to 73 years old from the general population of the United Kingdom between 2006 and 2010 with a median nine years of follow-up. HDL-C levels >80 mg/dL were strongly associated with increased risk of all-cause death (HR 1.8; CI, 1.6–2.0) and CV death (HR 1.9; CI, 1.5–2.4) in men. This association was also significant after adjusting for age, race, BMI, hypertension diagnosis, smoking history, triglycerides, LDL-C level, stroke history, heart attack history, diabetes diagnosis, eGFR, and alcohol use. HDL-C >80 mg/dL was not associated with an increased risk of all-cause or CV death in women. As the study's cohort is predominantly of European ancestry, results may not be generalizable to broader patient ethnicities.

A 2016 observational cohort study with 631,762 individuals enrolled in the Cardiovascular Health in Ambulatory Care Research Team dataset checked for an association between HDL-C and cause-specific mortality.[3] Patients were living in Ontario, between 40 and 105 years old, had no previous CV disease or severe comorbidities, and had an outpatient fasting cholesterol measurement in the previous year. Patients were a mean age of 57 years old, 55% were women, and the mean HDL-C level was 55 mg/dL. In total, 17,952 deaths were noted during the study, with an overall mortality of 8.1 per 1,000 person-years in men and 6.6 per 1,000 person-years for women. The mean follow-up duration was 4.9 years. The primary outcome was the association between HDL-C levels and mortality from CV and non-CV causes. Men with HDL-C levels >70 mg/dL had an increase in mortality from non-CV and noncancer etiologies (HR 1.3; CI, 1.2–1.6) but not CV and cancer mortality. This association was greatest at the highest cholesterol category (>90 mg/dL). Women with HDL-C >90 mg/dL had a significant increased risk of non-CV and noncancer deaths (HR 1.3; CI, 1.01–1.7) but no increased risk in CV or cancer mortality. Study limitations included a paucity of information on lifestyle factors like smoking, alcohol, and BMI. Death determination also taken from death certificates and may have been prone to misclassification. EBP

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For adult patients hospitalized with acute pancreatitis, does treatment with moderate intravenous fluids improve outcomes compared with treatment with aggressive intravenous fluids?

EVIDENCE-BASED ANSWER

No significant difference is noted in in-hospital mortality between moderate or aggressive volumes of intravenous fluids in the treatment of acute pancreatitis, but treatment with moderate fluids is associated with small reductions in the risk of organ failure, renal complications, and pulmonary complications, as well as a modestly decreased length of hospital stay by a few days (SOR: **B**, a meta-analysis of randomized controlled trials and prospective and retrospective cohort studies). Intravenous fluid therapy in acute pancreatitis should be goal-directed using specific clinical and biochemical measures of perfusion (SOR: **C**, expert recommendation from practice guideline).

DOI 10.1097/EBP.0000000000002139

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

In 2023, a meta-analysis of 14 studies (N=3,852), including five randomized controlled trials (N=513), eight retrospective cohort studies (N=3,092), and one prospective cohort study (N=247), compared treatment with moderate intravenous fluids with aggressive intravenous fluids in adult patients hospitalized with acute pancreatitis.[1] Most patients had acute pancreatitis from gallstones, whereas the second most common etiology was alcohol use. Significant heterogeneity among studies was noted when defining moderate fluids, aggressive fluids, and disease severity, the last of which was not reported. Some studies defined aggressive fluids as greater than or equal to four liters in the first 24 hours and moderate fluids as less than four liters in the first 24 hours; other studies defined aggressive fluids as an initial 20 mL/kg bolus followed by a 3 mL/kg/h infusion and moderate fluids as an initial 10 mL/kg bolus followed by a 1.5 mL/kg/h infusion. In-hospital mortality was the primary outcome measured, and secondary outcomes included pancreatic necrosis, organ failure, renal complications (acute kidney injury, creatinine >1.9 mg/dL, or renal failure), pulmonary complications (new-onset respiratory distress, PaO_2/FiO_2 ratio <300, or respiratory failure), and length of stay. Analysis revealed no significant difference in in-hospital mortality between aggressive fluids and moderate fluids (11 studies, N=2,725; relative effect [RE] 1.2; 95% CI, 0.83–1.9; I^2=34%). Compared with moderate fluids, aggressive fluids showed significantly higher rates of organ failure (9 studies, N=1,786; RE 1.6; 95% CI, 1.1–2.3; I^2=48%) and renal complications (7 studies, N=1,978; RE 1.7; 95% CI, 1.3–2.2; I^2=15%). When comparing length of stay, aggressive fluids had a mean of 17.5 days, and moderate fluids had a mean of 13.9 days (7 studies, N=1,281; P<.00001; I^2=0%). Initially, pooled results for pulmonary complications did not show a difference between groups, but significant heterogeneity was noted in this outcome (I^2=96%). Removing the two studies that led to most of the heterogeneity, aggressive fluids increased the risk of pulmonary complications (6 studies, N=918; RE 1.5; 95% CI, 1.1–1.8; I^2=5%). No significant difference in rates of pancreatic necrosis was seen in moderate versus aggressive fluids. Limitations included the fact that 11 of the 20 trials used a retrospective observational design and definitions of aggressive fluids, moderate fluids, disease severity, and length of treatment varied among trials.

In 2018, the American Gastroenterological Association issued a guideline on the initial management of acute pancreatitis based on data from limited clinical trials and expert opinion.[2] For patients with acute pancreatitis, they recommended using goal-directed therapy, defined as titration of IV fluids to specific clinical and biochemical targets of perfusion for fluid management, such as heart rate, mean arterial pressure, central venous pressure, urine output, blood urea nitrogen concentration, and hematocrit. They also recognized that

aggressive fluid therapy could lead to harm, including respiratory complications and abdominal compartment syndrome. The quality of evidence for these recommendations was deemed very low and their strength of recommendation conditional. EBP

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Should pregnant patients fast before their one-hour glucose tolerance test?

EVIDENCE-BASED ANSWER

No. Pregnant individuals with singleton pregnancies at 24 weeks of gestational age or later screened positive less often when eating within two hours before 50-g one-hour glucose tolerance test (GTT; SOR: **B**, randomized controlled trial). A nonfasting test is appropriate when performing the 50-g one-hour GTT (SOR: **B**, evidence-based guideline).

DOI 10.1097/EBP.0000000000002136

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

A 2023 randomized control trial (n=200) compared the positivity rate of the 50-g one-hour oral glucose tolerance test (GTT) in fasting versus nonfasting patients with singleton pregnancies at 24 weeks or greater with no previous diagnosis of gestational diabetes (GDM).[1] Fasting was defined as no oral intake for greater than six hours. Nonfasting was defined as oral intake within two hours. This was a single-center study, and it was not blinded because of the nature of the study design. Time and type of last oral intake before the test was confirmed with a survey completed the day of or the day after the test. Randomization included both high-risk and average-risk patients. Positive testing was defined as a blood glucose level between 140 and 179 mg/dL. Any patient with positive testing underwent a fasting 100-g three-hour GTT to determine the diagnosis of GDM. Any blood glucose level >180 mg/dL indicated a presumptive diagnosis of GDM and that individual did not undergo the 100-g three-hour test. A higher percentage of patients in the fasting group met criteria for the second step of screening (32% vs 13%; absolute difference of 19%; 95% CI, 7.2–30%). The authors did not comment on the type of oral intake in their analysis. Notably, the study was underpowered to detect a difference in GDM diagnosis or in maternal/neonatal outcomes.

The United States Preventive Services Task Force (USPSTF) commissioned a systematic review of 45 prospective studies concerning screening methods for GDM, including the 50 g one-hour GTT, to develop their 2021 evidence-based guidelines.[2] The guidelines indicated that this is an appropriate screening test for GDM (strength of recommendation B), and that this test is performed in the nonfasting state. EBP

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In postmenopausal women with osteoporosis, is denosumab better at preventing axial and appendicular fractures than bisphosphonates?

EVIDENCE-BASED ANSWER

No, but comparable. Denosumab and bisphosphonates perform similarly in fracture risk reduction in postmenopausal women. Although denosumab outperforms bisphosphonates in increasing bone mineral density, it does not clinically lead to better fracture reduction. (SOR: **A**, multiple systematic reviews and meta-analyses).

DOI 10.1097/EBP.0000000000002134

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

A 2023 systematic review and meta-analysis evaluated the efficacy and safety of osteoporosis drugs in preventing vertebral fractures.[1] The study included 92 trials, with 55 randomized controlled trials (RCTs) published through February 2021. Based on the total pooled population and pharmacotherapies, 145,516 postmenopausal women with osteoporosis (based on a T-score of <–2.5) and 16 unique drugs were included. The 55 RCTs (N=104,580) examined 16 different pharmacotherapies for osteoporosis compared with placebo or one another using a surface under the cumulative ranking curve (SUCRA) ranking. The follow-up period was variable but ranged from 18 to 72 months. Compared with placebos, denosumab (risk ratio [RR] 0.30; 95% CI, 0.14–0.61) and three bisphosphonates (alendronate [RR 0.55; 95% CI, 0.38–0.81], risedronate [RR 0.65; 95% CI, 0.42–1.00], zoledronate [RR 0.41; 95% CI, 0.26–0.65]) all reduced the risk of vertebral fractures. Subgroup analysis found that short-term (≤18 months) vertebral fracture risk was reduced in patients treated with the three bisphosphonates: alendronate (RR 0.34; 95% CI, 0.20–0.58), risedronate (RR 0.45; 95% CI, 0.34–0.61), zoledronate (RR 0.30; 95% CI, 0.21–0.44), and denosumab (RR 0.12; 95% CI, 0.03–0.56). Using SUCRA ratings, denosumab (SUCRA: 0.78) performed third best overall and second best within the first 18 months in preventing osteoporotic vertebral fractures and was ranked above all bisphosphonates included. The only major limitation of this study was the heterogeneity of the individual studies, most notably in their time points, making the follow-up period assessment difficult.

A 2012 systematic review and meta-analysis of four double-blinded international multicentered RCTs (N=1,942) directly compared denosumab 60 mg subcutaneously every six months with oral alendronate 70 mg oral weekly in postmenopausal women with osteoporosis.[2] The authors assessed the quality of outcomes based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines. At one-year follow-up, both drug regimens showed low-quality evidence of fracture risk reduction, with alendronate insignificantly out-performing denosumab (odds ratio 1.42; 95% CI, 0.84–2.40; P=.19). All four studies showed improved bone mineral density (BMD) in the lumbar spine, two of four studies showed improved BMD in the femoral neck, and another two of four studies showed improved BMD in the distal radius. Both treatments improved BMD at 12 months; however, denosumab improved BMD more than alendronate in all studies (P<.005–.001). To assess the safety of each regimen, hazard ratios of denosumab versus alendronate were assessed for neoplasms and infection rate, both of which were similar between denosumab and alendronate. One major limitation of this study was the cohort included T-scores ranging from –1.6 to –2.4 (osteopenia), which decreased the strength of evidence for osteoporotic women but increased generalizability. In addition, the average age was relatively young of osteoporosis cases (60–68 years old).

A 2016 systemic review and meta-analysis of five RCTs (N=3,751) assessed studies comparing denosumab versus bisphosphonates in postmenopausal

women.[3] Two studies compared subcutaneous denosumab 60 mg versus oral alendronate 70 or 35 mg. One study compared varying doses of denosumab (6, 14, or 30 mg every 3 months; denosumab 14, 60, 100, or 210 mg every 6 months) versus alendronate (70 mg once weekly).One compared denosumab (60 mg SQ every 6 months) versus risedronate (150 mg orally every month). One compared denosumab (60 mg SQ every 6 months) versus ibandronate (150 mg orally every month). Two of the studies had a two-year treatment duration, and three studies had a one-year duration. Four of the five studies analyzed fracture rates, and all found no difference between the groups. The denosumab fracture risk percent for the four studies averaged 2.7% (3.8%, 3%, 2.5%, and 1.5%). The bisphosphonates fracture risk percentage averaged 2.25% (4.3%, 2.2%, 1.4%, and 1.1%). However, denosumab outperformed bisphosphonates in increasing bone mineral density at varying sites (5 of 5 RCTs) and more rapid reduction of bone turnover markers (4 of 5 RCTs). No difference was noted in serious adverse events, including infection rates (3 of 5 RCTs). The major limitation of this meta-analysis was that the RCTs did not have fracture risk as their primary outcome, which led to this meta-analysis being underpowered to directly compare fracture rates between groups. EBP

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Does turmeric supplementation reduce osteoarthritis pain?

EVIDENCE-BASED ANSWER

Curcumin (the active ingredient in turmeric) supplementation is more effective than placebo and as effective as NSAIDs in reducing knee osteoarthritis pain (SOR: **B**, meta-analysis of low-quality randomized controlled trials [RCTs]). In combination with NSAIDs, it seems to reduce knee pain scores more than NSAIDs alone (SOR: **B**, meta-analysis of low-quality RCTs). Turmeric supplementation has a lower risk of adverse events compared with NSAIDs (SOR: **B**, systematic reviews and meta-analyses of low-quality RCTs).

DOI 10.1097/EBP.0000000000002121

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

A 2022 meta-analysis of 15 randomized controlled trials (RCTs; N=1,670) evaluated the effects of curcumin on pain in patients with knee osteoarthritis (OA) compared with placebo or NSAIDs.[1] Patients were diagnosed with knee OA according to the American College of Rheumatology criteria. Researchers assessed pain on a visual analog scale (VAS, range 0–10; minimum clinical important difference 1.18) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale (range 0–20; minimum clinically important difference 2.12) each, where a higher score indicates more pain. Patients received curcumin (80–2,000 mg per day), NSAIDs (ibuprofen or diclofenac), or placebo for four weeks to six months. In comparison with placebo, curcumin significantly improved VAS knee pain ratings (9 studies, n=598; weighted mean difference [WMD] –1.8; 95% CI, –2.4 to –1.1; I^2=87%) but did not reach a clinically meaningful change in WOMAC pain scores (6 studies, n=481; WMD –1.9; 95% CI, –2.9 to –0.97, I^2=79%). No significant difference was noted between groups treated with curcumin and NSAIDs in improvement of VAS

pain ratings (3 studies, N=272; WMD –0.3; 95% CI, –0.63 to 0.04, I^2=6.3%) or WOMAC pain scores (2 studies, N=475; WMD 0.24; 95% CI, –0.47 to 0.96, I^2=0.0%). No significant difference was noted in adverse event incidence between curcumin and placebo or NSAID group. The most common adverse effects reported were dyspepsia, nausea, and stomach pain. Limitations included overall low quality of RCTs with significant heterogeneity of data (I^2 values >50% for many outcomes), and many of the included trials were industry funded.

A 2022 meta-analysis of 14 RCTs of 1,533 patients compared curcumin with conventional therapies on the treatment of OA.[2] The study included patients with knee OA, with most studies conducted in India and Thailand. Patients received curcumin alone (80–1,500 mg per day), curcumin combined with NSAIDs, or NSAIDs alone. Studies comparing curcumin to placebo were excluded. Seven of the included trials overlapped with the previous meta-analysis. Duration of treatment ranged from four weeks to four months. Primary outcomes were VAS and WOMAC pain scores. A large reduction was noted in VAS scores with curcumin combined with NSAIDs in comparison with NSAIDs alone (4 studies, N=418; standard mean difference [SMD] 5.8; 95% CI, 2.2–9.4; I^2=99%). A large reduction of WOMAC pain scores was also noted in the combined group in comparison with NSAIDs alone (3 studies, N=388; SMD 0.84; 95% CI, 0.22–1.5; I^2=88%). The overall incidence of adverse events was lower in the combined group in comparison with the NSAID-only group (4 studies, N=418; odds ratio [OR] 0.28; 95% CI, 0.14–0.58; I^2=0%), including rates of dyspepsia (4 studies, N=418; OR 0.17; 95% CI, 0.03–0.97; I^2=16%), nausea/vomiting (4 studies, N=418; OR 0.28; 95% CI, 0.11–0.74; I^2=0%), and abdominal pain (4 studies, N=418; OR 0.16; 95% CI, 0.05–0.49). Limitations included the small number of studies included, high heterogeneity of data, and again many industry-funded studies. EBP

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Does treatment with CPAP reduce atrial fibrillation in patients with AF and obstructive sleep apnea?

EVIDENCE-BASED ANSWER

Overall, continuous positive airway pressure (CPAP) treatment may reduce the recurrence or progression to permanent atrial fibrillation (AF) in those with obstructive sleep apnea (OSA) compared to OSA patients not using CPAP (SOR: **B,** meta-analysis of primarily cohort studies with limitations). However, there does not seem to be a reduction in AF burden after CPAP therapy in patients with moderate-to-severe OSA (SOR: **B**, single randomized controlled trial).

DOI 10.1097/EBP.0000000000002132

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

In 2021, a meta-analysis of five prospective cohort studies, three retrospective cohort studies, and one randomized controlled trial (RCT; N=14,812) evaluated the recurrence or progression of atrial fibrillation (AF) in continuous positive airway pressure (CPAP) using and non-CPAP using patients with and without obstructive sleep apnea (OSA; N=14,812; 1,176 used CPAP, 987 did not use CPAP, and 8,887 did not have OSA).[1] OSA was variably defined as having an apnea–hypopnea index greater than 5 to 15 per hour and diagnosed by polysomnography. Follow-up ranged from seven months to two years with AF recurrence diagnosed by ECG and

Holter or event monitoring. AF progression was defined as paroxysmal or new-onset becoming permanent by the last follow-up. Variable numbers of patients received other interventions for AF including rate control and radiofrequency ablation. CPAP usage, which was mostly patient defined, decreased the risk of AF progression or recurrence compared with no CPAP in those with OSA (9 studies; N=2,163; 25% vs 41%; RR 0.7; 95% CI, 0.57–0.85; *P*=.04). AF progression or recurrence was similar in the OSA group treated with CPAP compared with the non-OSA group. Limitations included use of observational studies, variability in diagnosis and type of AF, ablation criteria, CPAP compliance, and severity of OSA.

A 2021 open-label parallel-group RCT (n=108) evaluated the effect of CPAP therapy on AF burden in patients referred for catheter ablation of paroxysmal AF or recruited from AF outpatient clinics who were screened for OSA.[2] Eligible patients were diagnosed with moderate-to-severe central or OSA (apnea–hypopnea index >15/hour). Patients had a mean age of 63 years old and 76% were male. Paroxysmal AF was defined as recurrent episodes of AF that terminated spontaneously or were cardioverted within seven days. Researchers excluded patients with an ejection fraction less than 45%, BMI >40 kg/m^2, or Epworth Sleepiness Scale score >15. Patients underwent a trial of CPAP tolerance before loop recorder implantation. Baseline AF burden was assessed for four weeks. Patients were then randomized 1:1 to receive auto-titrating CPAP (n=55) or to continue usual care (n=54) for five months. Neither investigators nor patients were blinded; however, outcome assessments were blinded. The primary outcome was change in AF burden, defined as percentage of time in AF, measured by loop recorder from baseline to the last three months of the intervention period. No difference was noted in AF burden between groups. Patients with poor adherence (using device <4 hours per night) were excluded before randomization, leading investigators to conclude that the effect was not influenced by adherence to CPAP. Limitations included small sample size, open-label design, decreased generalizability, using respiratory polygraphy instead of polysomnography which may underestimate OSA severity, and short study duration. EBP

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How effective and safe are hyaluronic acid injections for pain and function in patients with knee osteoarthritis?

EVIDENCE-BASED ANSWER

For patients with knee osteoarthritis (OA), viscosupplementation (intra-articular hyaluronic acid injection) provides small statically significant improvements in knee pain and function deemed to not be clinically significant and is associated with a 50% increase in serious adverse events as compared with placebo injections (SOR: **A**, systematic review and meta-analysis of randomized controlled trials). Guidelines recommend against routine use of viscosupplementation for patients with knee OA but acknowledge that it may be considered for occasional patients who have failed other therapies (SOR: **C**, evidence-based guidelines with inconsistent recommendations).

DOI 10.1097/EBP.0000000000002060

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

A 2022 systematic review and meta-analysis of 25 randomized controlled trials (RCTs; N=9,423) evaluated the effectiveness and safety of viscosupplementation for pain and function in adult patients with knee osteoarthritis.[1] Patients were on average 62 years old; 59% were female and the average disease duration was 5.2 years. All had clinically or radiographically confirmed knee osteoarthritis of varying severities. Patients in the treatment arm of each study received a median of three (interquartile range 1–5) intra-articular injections of various preparations of hyaluronic acid (low, intermediate, or high molecular weight, cross-linked or non–cross-linked) or hyaluronic acid derivatives. The control group received a placebo injection (saline or negligible amounts of hyaluronic acid) or no intervention. The primary outcome was pain intensity measured as a continuous variable and analyzed as a standardized mean difference (SMD); negative values indicated improved pain with viscosupplementation versus control. An SMD of −0.37 was deemed the minimal clinically important difference (MCID) and corresponded to a −9-mm change on a 100-mm visual analog scale (VAS). A secondary outcome was function, measured with Lequesne or Western Ontario and McMaster Universities Arthritis indices and similarly analyzed as an SMD, with an MCID of −0.37. The median follow-up after the last injection was 13 weeks for pain and 12 weeks for function. Another secondary outcome was the risk of serious adverse events. Pooled results revealed that the treatment group experienced a small, statistically significant but not clinically relevant reduction in pain intensity (24 RCTs, N=8,997; SMD −0.08; 95% CI, −0.15 to −0.02) as compared with the control group; the estimated change using a 100-mm VAS was −2 mm (95% CI, −3.8 to −0.5 mm). Pooled results also demonstrated a small, not clinically relevant, functional improvement in the treatment arm (19 RCTs, N=6,307; SMD −0.11; 95% CI, −0.18 to −0.05) when compared with the controls. The pooled data showed a 50% increased risk of serious adverse events for viscosupplementation compared with the controls (15 RCTs, N=6,462; relative risk 1.5; 95% CI, 1.1–2.0).

A 2021 consensus and evidence-based guideline on nonarthroplastic management of knee osteoarthritis from the American Academy of Orthopedic Surgeons recommended against the routine use of intra-articular hyaluronic acid injections for symptom control (moderate SOR based on 2 or more moderate-quality studies with consistent findings).[2] The guideline authors acknowledged that some studies showed statistically significant improvement but failed to demonstrate a MCID, suggesting that viscosupplementation injections could be considered in some patients who had failed other treatments.

A 2019 consensus and evidence-based guideline from the American College of Rheumatology and the Arthritis Foundation for the management of osteoarthritis of the hand, hip, and knee recommended against intra-articular knee injections of hyaluronic acid (conditional recommendation against, based on a systematic review of clinical trials).[3] The guideline authors noted that the best evidence failed to show a benefit of hyaluronic acid injections but recognized that viscosupplementation could be considered for patients who had exhausted other conservative treatments, after a discussion of the limited evidence for benefit.

A 2019 Osteoarthritis Research Society International guideline for the nonsurgical management of knee, hip, and polyarticular osteoarthritis made a conditional recommendation in favor of intra-articular hyaluronic acid injections for adults with knee arthritis with or without comorbidities (level 2; conditional recommendation based on a systematic review followed by consensus voting with 60–74% in favor).[4] EBP

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Is *Helicobacter pylori* eradication effective for prevention of peptic ulcer bleeding in adult patients using aspirin?

EVIDENCE-BASED ANSWER

Primary eradication of *H pylori* to prevent peptic ulcer bleeding in patients 60 years old and older using aspirin results in a statistical but not clinically significant reduction in peptic ulcer bleeding within the first 2.5 years of treatment. This effect does not last beyond 2.5 years (SOR: B, single randomized controlled trial). Daily aspirin users with a history of peptic ulcer bleeding who were positive for *H pylori* and successfully eradicated have similar episodes of recurrent bleeding as aspirin-naïve patients. However, in *H pylori*-negative patients with aspirin-associated bleeding have a higher incidence of recurrent bleeding. (SOR: B, prospective cohort study). The American College of Gastroenterology recommends testing for *H pylori* before initiation of long-term aspirin therapy (SOR: C, expert opinion).

DOI 10.1097/EBP.0000000000002114

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

A 2022 double blind randomized controlled trial assessed the effect of *H pylori* eradication for the primary prevention of peptic ulcer bleeding in older patients taking daily aspirin in the primary care setting.[1] The study assessed adults at least 60 years old receiving 325 mg aspirin a day or less with a positive *H pylori* C13 urea breath test. Patients were randomized 1:1 into treatment (n=2,677) and placebo control (n=2,675) groups. Patients who were already taking nonsteroidal anti-inflammatory medications or any gastroprotective medications at the initial screening visit were excluded, although these medications could be added if clinically indicated during the course of the study. Patients were contacted annually after randomization until either death or the end of the study in June 2020, a median of five years and maximum of eight years. In addition, investigators searched multiple electronic health records, health registries, and databases during the follow-up period for any encounters that mentioned "gastrointestinal bleeding" or "peptic ulcer." Those encounters were reviewed by an adjudication committee blinded to therapy consisting of three specialist clinicians. Analysis of the records revealed primary eradication of *H pylori* prevented peptic ulcer bleeding within 2.5 years compared with placebo with six episodes in the treatment group versus 17 episodes in the control group (hazard ratio [HR] 0.35; 95% CI, 0.14–0.89; ARR 0.42%; NNT=238). Beyond 2.5 years, no significant differences were observed between the groups (HR 1.3; 95% CI 0.55–3.1). Limitations included low rates of outcome events, possibly because guidelines recommending fewer patients use long-term aspirin therapy before the end of the study. In addition, confirmation of aspirin usage was only tracked by prescriptions, not observed usage.

A 2013 prospective cohort study of aspirin users with peptic ulcer bleeding evaluated the effect of *H pylori* infection on recurrent ulcer bleeding.[2] Three cohorts were followed: (1) aspirin users with peptic ulcer bleeding and *H pylori* infection that was successfully eradicated (n=249); (2) aspirin users with peptic ulcer bleeding without *H pylori* infection (n=118); and (3) aspirin-naïve patients without a history of peptic ulcer now started on aspirin for cardiothrombotic disease (average-risk cohort, n=537). The three cohorts were re-evaluated every three to six months for gastroduodenal bleeding for up to 10 years. The results demonstrated no decrease in mortality from GI bleeding among the three cohorts (P=.14). The rate of recurrent ulcer bleeding was not significantly different between *H pylori* eradicated and average-risk cohorts (incidence rate ratio 1.47, 95% CI 0.75–3.38). The incidence of recurrent bleeding ulcers in the H. pylori-negative cohort (incidence rate [IR] 5.22%, 95% CI 3.04–8.96%) was five

times higher than in the H. pylori-eradicated cohort (IR 0.97%, 95% CI 0.53–1.80%) and 8 times higher than in the average-risk cohort (IR 0.66%, 95% CI 0.38–0.99%). In patients taking aspirin, the addition of proton pump inhibitors or histamine-2-receptor antagonists to the *H pylori* negative cohort showed a 6-fold reduction (IR 0.86%, 95% CI 0.21–3.50) in the incidence of ulcer bleeding. However, concomitant use of antiulcer medications did not make a significant difference in ulcer bleeding in the average risk cohort, the H. pylori-eradicated cohort, or the H. pylori-negative cohort where other medications that cause bleeding were used in addition to aspirin. The study demonstrated that daily aspirin users with previous bleeding ulcers and eradicated *H pylori* infection had reduced recurrence of ulcer bleeding, similar to the incidence found in the average-risk cohort. While this study allowed longer cohort follow-up than previous studies, the fact that it was limited to the ethnic Chinese population of Hong Kong limits the applicability to more homogenous populations such as the United States.

The American College of Gastroenterology (ACG) in 2017 recommended testing for *H pylori* before initiation of long-term aspirin therapy.[3] The recommendation was based largely on the endoscopic observational study above. The ACG acknowledged at that time that there had not yet been a prospective randomized trial addressing eradication of *H pylori* in a population similar to the United States and that evidence for this recommendation was of low quality. EBP

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Do intra-articular ketorolac injections provide similar relief to corticosteroid injections in patients with knee and hip osteoarthritis?

EVIDENCE BASED ANSWER

Yes. In patients with moderate knee or hip arthritis, both ketorolac and triamcinolone similarly provide an improvement in pain and function at one but not three months. Results are not clinically meaningful (SOR: B, single, randomized noninferiority trial). As adjunctive therapy, both triamcinolone and ketorolac with sodium hyaluronate injection improve knee pain and function at three months (SOR: C, 2 case-control studies).

DOI 10.1097/EBP.0000000000002122

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

A 2021 double-blinded, randomized, noninferiority trial examined the efficacy of ketorolac and triamcinolone injections of the hip and knee to improve pain and function.[1] In the study, 110 patients with hip or knee osteoarthritis, mean age 65 years old, received a single ultrasound-guided injection of 5 mL 0.5% ropivacaine with either 80 mg triamcinolone or 30 mg of ketorolac. Exclusion criteria included pregnancy or lactation, knee or hip injection within the previous months, traumatic osteoarthritis or ligamentous reconstruction, chronic narcotic use, and inflammatory or neuropathic arthropathy. The trial surveyed patient's pain and function at 1, 4, and 12 weeks postinjection using the modified visual analog score (VAS) 1 to 10 for severe pain; minimum clinically important difference (MCID) 3, and Hip Osteoarthritis and Outcome Scores (HOOS Jr), where 0 is perfect hip health to 24 total disability which is then converted to a 0 to 100 point scale; the MCID is 18. Comparing baseline and one month postinjection, the ketorolac and triamcinolone groups had statistical improvement in hip pain by VAS (ketorolac 5.3 vs 4.2; $P<.05$; and triamcinolone 5.4 vs 3.7; $P<.05$) and function by HOOS Jr (ketorolac 10.9 vs 7.7; $P<.05$; and triamcinolone 11.4 vs 7.7; $P<.05$). By three months postinjection, there was no longer any statistical improvement in pain or function in either group. Side effects of both groups were mild. There were no significant differences in outcomes between drug groups. Limitations include moderate sample size, subjectivity in pain scores, large dose of triamcinolone, and relatively short follow-up.

A 2022 retrospective case-control study evaluated patients with symptomatic knee osteoarthritis receiving a knee injection of either ketorolac or corticosteroid.[2] Fifty patients, mean age 59 years old, and mean body mass index of 21 kg/m^2, with symptomatic knee osteoarthritis were enrolled, all after failing medical or physical therapy for three months. Researchers excluded patients with a history of trauma, NSAID use two days before injection, corticosteroid injection in the last six months, prior knee surgery, and any injection in the knee in the preceding three months. Patients received injections of either 40 mg of triamcinolone or 10 mg of ketorolac with lidocaine weekly for three weeks. At the fourth week, all patients received an intra-articular sodium hyaluronate injection and three days of NSAID and oral antibiotic. Patients were assessed for pain with VAS and function with Western Ontario and McMaster Universities osteoarthritis index (WOMAC) at baseline and weeks 1, 2, 5, and 12 after the first injection. The WOMAC is a 0 to 100-point scale (higher score, less impairment) measuring pain, stiffness, and function with a MCID for pain of 4.2 and function 10.1. Both groups had statistically and clinically significant improvement in pain and increased function (*P* not provided). The triamcinolone group had a reduction in pain (VAS 7.2–2.5 at week 1 and 2.2 at week 12) and improvement in function (WOMAC 48–23 at week 12). Similarly, the ketorolac group pain scores improved (VAS 7.8–3.1 at week 1 and 2.5 at week 12) as did function (WOMAC 49–23 at 12 weeks). No significant differences were observed in scores between groups. Side effects included inflammation and pain in two patients, which subsided after three days of analgesic, ice, compression, and rest. Limitations of the study included smaller sample size and confounding additions of hyaluronic acid injections and oral NSAIDs to the success of the outcome.

A 2020 case-control retrospective comparison study evaluated whether ketorolac and triamcinolone injections, when added to hyaluronic acid, improved pain and function in patients with osteoarthritis.[3] Eighty-four patients, mean age 59 years old, with unilateral symptomatic knee osteoarthritis, were divided into two groups. Patients received three weekly injections of 0.5% lidocaine, 25 mg of sodium hyaluronate, and either 25 mg of triamcinolone acetonide or 10 mg of ketorolac. Then, both groups received two injections containing 0.5% lidocaine and 25 mg of sodium hyaluronate a week apart. Researchers excluded patients with inflammatory knee arthritis, autoimmune diseases, and injection in the knee three months prior. Pain, function, and side effects were measured baseline and at weeks 1, 2, 5, and 12 after last injection with VAS and WOMAC scores. Both groups had a statistically and clinically significant improvement in pain and function from baseline to 12 weeks. Pain scores improved similarly in the triamcinolone (VAS 7.2–2.2, no *P* value given) and ketorolac groups (VAS 7.4–2.3, no *P* value given). By 12 weeks, function improved in the triamcinolone (WOMAC 47–23, $P<.001$) and ketorolac (WOMAC 48–22, $P<.001$) groups. No significant differences in pain or function scores between groups were found at 12 weeks. Oral imrecoxib was permitted for three days after each injection. Adverse reactions included local site pain in three patients in the ketorolac group. Limitations of the study included possible confounding additions of posodium hyaluronate and oral NSAID and varying ketorolac doses. EBP

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The authors declare no conflicts of interest.

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