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EVIDENCE-BASED PRACTICE

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Family Physicians Inquiries Network

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TABLE OF CONTENTS

VOL 27 | NO. 8 | August 2024

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

DIVING FOR PURLs

GEMS

IN DEPTH

HELPDESK ANSWERS

SPOTLIGHT ON PHARMACY

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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

Statements and opinions expressed in articles and communications in this journal are those of the author(s) and not necessarily those of the editor, publisher, or any organizations endorsing this journal. The Publisher and editors of EBP do not endorse any methods, products, or ideas mentioned in the journal, and disclaim any liability which may arise from any material herein. Unless noted, authors have reported no competing interests and have nothing to disclose.

DISCLOSURE

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Cannot stand a statin? Consider bempedoic acid

Nissen SE, Menon V, Nicholls SJ, et al. Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients. *JAMA*. 2023; 330(2):131-140. doi: 10.1001/jama.2023.9696

doi: 10.1097/EBP.0000000000002128

This prespecific subgroup analysis of a larger double-blind, randomized, multicenter clinical trial compared bempedoic acid with placebo among 4,206 statin intolerant patients with significant risk factors for cardiovascular disease. Patients had one of the following risk factors for cardiovascular disease: a coronary artery calcium score >400 Agatston units, male age older than 60 years old or female age older than 65 years old with diabetes, a Systematic Coronary Risk Evaluation (SCORE) risk >7.5%, or Reynolds Risk Score >30% over 10 years. Statin intolerance was defined as an adverse event after starting or increasing the dose of a statin medication that improved after discontinuation of the statin. After a four-week single-blind, placebo run-in period, patients were randomized to either 180 mg bempedoic acid daily or placebo was for a median of 40 months. The primary composite outcome included nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or death. Secondary endpoints included 3-component major adverse cardiovascular events (cardiovascular death, nonfatal MI, nonfatal stroke), fatal or nonfatal MI, coronary revascularization, fatal or nonfatal stroke, cardiovascular death, all-cause mortality, and adverse events. A total of 5.3% of patients in the bempedoic acid group as compared with 7.6% of patients in the placebo group met the primary outcome (hazard ratio [HR] 0.70; 95% CI, 0.55–0.89, NNT=43). Rates of the 3-component MACE and all-cause mortality were lower in the bempedoic acid group as compared with placebo (4.0% vs 6.4%, HR 0.64; 95% CI, 0.48–0.84, NNT=42, and 3.6% vs 5.2%, HR 0.73; 95%, 0.54–0.98, NNT=63, respectively). The rate of treatment discontinuation was high for both the bempedoic acid and placebo groups (27% vs 32%, respectively). Fatal and nonfatal MI, stroke, coronary revascularization, serious adverse events, and adverse events leading to discontinuation were similar between the two groups. The bempedoic acid group had a higher rate of elevated liver enzymes (4.5% vs 2.6%) and kidney impairment (10.3% vs 8.1%) as compared with placebo.

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 PubMed with the terms "primary prevention" and "statin intolerance" to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: Among patients at high risk of cardiovascular disease with statin intolerance, bempedoic acid may reduce the risk of cardiovascular events and possibly all-cause mortality. These data should be considered hypothesis generating because this was a subgroup analysis of a larger trial; nevertheless, the results still provide hope for effective therapy for high-risk statin-intolerant patients.

Mayuri Jagadish, MD
Carina Brown, MD
Cone Health Family Medicine Residency

The Corresponding Faculty Author is: Carina Brown; carina.brown@conehealth.com
The authors declare no conflict of interest.

Antenatal corticosteroids: Helpful or Harmful?

Citation: Ninan K, Gojic A, Wang Y, et al. The proportions of term or late preterm births after exposure to early antenatal corticosteroids, and outcomes: systematic review and meta-analysis of 1.6 million infants. *BMJ*. 2023; 382: e076035. doi:10.1136/bmj-2023-076035

doi: 10.1097/EBP.0000000000002157

This was a systematic review and meta-analysis looking at randomized control trials (RCTs) and population-based cohort studies between January 1, 2000, and February 1, 2023, with data on infants with early exposure to antenatal corticosteroids (<34 weeks of gestation) but born at term ($\geq$37 weeks of gestation), late preterm (34 0/7–36 6/7 weeks of gestation), or term/preterm combined. The primary outcome for the study was the proportion of infants born at term who had early exposure to antenatal corticosteroids. The secondary outcomes included proportion of infants born at late preterm or term/late preterm combined, short-term and long-term outcomes for the infants exposed to early antenatal corticosteroids, and outcomes in pregnant people. Seven RCTs and 10 population-based cohort studies, with a combined total of greater than 1.6 million children, were included in the analysis. In the population-based cohort studies, 45% of infants with early exposure to antenatal corticosteroids were born at term (95% CI, 0.44–0.46). In the RCTs, the proportion of infants born at term after early exposure to 1 course or dose of antenatal corticosteroids was 37% (95% CI, 0.30–0.44) in singleton deliveries. Reviewing RCTs comparing a single dose with repeated courses of corticosteroids in singletons and multiples, a lower proportion of term births was observed in repeated doses: 10% (95% CI, 0.08–0.12) versus 19% (95% CI, 0.16–0.23). Early exposure to antenatal corticosteroids in infants born at term had the following adverse adjusted secondary short-term outcomes: neonatal intensive care unit admission, adjusted odds ratio (aOR) of 1.49 (95% CI, 1.19–1.86); small for gestational age, aOR 1.78 (95% CI, 1.48–2.14); and reduced head circumference, adjusted mean difference --0.21 cm (95% CI, –0.29 to –0.13 cm). Any long-term mental or behavioral disorder if born at term with early antenatal exposure of corticosteroids was found to have an adjusted hazard ratio of 1.47 (95% CI. 1.36–1.60). The certainty of evidence for these results were found to be low to very low by the GRADE criteria, except for the proportion of infants born at term/late preterm (combined) was found to have a high level of certainty.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching Dynamed, USPSTF, UpToDate, and ACOG with the term "antenatal corticosteroids" to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: The study found that approximately 40% of infants are born at term after early exposure to antenatal corticosteroids, and exposure is associated with short-term and long-term adverse outcomes; however, the evidence was low to very low certainty, and association does not indicate causality.

Amanda J. Laska-Trump, MD
Ariel Hoffman, MD
Madigan Army Medical Center, US Army

The corresponding author is Ariel Hoffman; ariel.l.hoffman.mil@health.mil

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

Safety of Vaginal Estrogen in Breast Cancer Survivors

Agrawal P, Singh SM, Able C, et al. Safety of Vaginal Estrogen Therapy for Genitourinary Syndrome of Menopause in Women With a History of Breast Cancer. *Obstet Gynecol*. 2023;142(3): 660-668. doi:10.1097/AOG.0000000000005294

doi: 10.1097/EBP.0000000000002159

This retrospective cohort study utilizing electronic health record and insurance claims data from the TriNetX research network evaluated breast cancer recurrence risk associated with vaginal estrogen therapy in women with a history of breast cancer diagnosed with genitourinary syndrome of menopause (GSM). Patients were women 18 years old or older diagnosed with GSM three months to five years after breast cancer diagnosis regardless of estrogen receptor (ER) status. Patients were excluded if diagnosed with active breast cancer requiring radiation, chemotherapy, or mastectomy within three months before GSM diagnosis or if diagnosed with any other primary malignancy within five years before or after GSM diagnosis. Investigators identified 42,113 women meeting criteria of which 5.0% had received vaginal estrogen; this included 10,584 women with known ER positive status of which 3.9% had received vaginal estrogen. Women were stratified into the vaginal estrogen cohort if they received at least three vaginal estrogen prescriptions within one year after GSM diagnosis and into the control cohort if they had not received vaginal estrogen within the same time frame. The vaginal estrogen cohort was compared with an equal number of patients in the control group using propensity score matching, accounting for age, race, family history, obesity, hormone therapy, and aromatase inhibitor use. The primary outcome was breast cancer recurrence, defined as the need for mastectomy, radiation, or chemotherapy, or diagnosis of secondary malignancy within three months to five years after initiation of vaginal estrogen. Secondary analyses included only women with ER-positive breast cancer, and a subanalysis evaluated the risk associated with concurrent aromatase inhibitor use. The overall breast cancer recurrence rate, regardless of ER status, was 17.6% in vaginal estrogen group and 17.1% in the control group (RR 1.03; 95% CI, 0.91–1.18). Women in the vaginal estrogen group had a lower risk of secondary malignancy (RR 0.52; 95% CI, 0.37–0.72). Similarly, among women with ER-positive breast cancer, no difference was observed in recurrence between the vaginal estrogen and control groups (30.6% vs 32.5%; RR 0.94; 95% CI, 0.77–1.15). However, risk of breast cancer recurrence for women with ER-positive breast cancer treated with vaginal estrogen was significantly higher with concurrent aromatase inhibitor use (76.3% vs 29.0%; RR 2.64; 95% CI, 1.55–4.47) with average time to recurrence in the concurrent AI group of 154 days.

Methods

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

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

Bottom line: This study adds to research needed to evaluate the safety of vaginal estrogen in breast cancer survivors with GSM. The use of vaginal estrogen for reducing genitourinary symptoms was not associated with an increase in breast cancer recurrence risk regardless of ER status. However, for women with a history of ER-positive breast cancer, concurrent aromatase inhibitor use was associated with a significantly higher risk of recurrence compared with vaginal estrogen use alone. This retrospective study was limited by use of medical record and insurance claims data without randomization, standardization of dosing, or detailed cancer staging. However, combined with recommendations from national guidelines, physicians can consider short-term low-dose vaginal estrogen therapy for those not on an aromatase inhibitor, despite boxed warning.

Jennifer Tarpenning, MD
Frances Tepolt, MD
University of Minnesota/CentraCare St. Cloud Family Medicine Residency

The corresponding author is Jennifer Tarpenning; jennifer.tarpenning@centracare.com.
The authors declare no conflict of interest.

Influenza Vaccination Not Associated With Increased Miscarriage Risk

Regan AK, Wesselink AK, Wang TR, et al. Risk of Miscarriage in Relation to Seasonal Influenza Vaccination Before or During Pregnancy. *Obstet Gynecol*. 2023;142(3): 625-635. doi:10.1097/AOG.0000000000005279

doi: 10.1097/EBP.0000000000002158

Investigators performed a secondary analysis of data from 2013 to 2022 in an ongoing large prospective cohort study of 6,946 women (18–45 years old) who were planning to conceive and included 1,135 male partners' vaccination data, at the invitation of female partner patients. Patients were recruited using advertisements on social media, websites, and parenting blogs. The influenza vaccinated cohort of women in this study included 1,398 (20.1% of total female cohort) women who were vaccinated within three months of becoming pregnant and 221 (3.2% of total female cohort) women vaccinated from weeks 4 to 19 of pregnancy. The cohort of patients in this study was 86% White and only 1.8% Black, non-Hispanic. Participants completed online baseline questionnaires, and the women participants were invited to complete follow-on questionnaires every eight weeks until pregnant, at early pregnancy (self-reported pregnancy), late pregnancy (around 32 weeks estimated gestational age [EGA]), and six months postpartum. Patients self-reported last menstrual period, EGA, influenza vaccination, and miscarriage (which was defined as spontaneous intrauterine pregnancy loss, including biochemical pregnancy and blighted ovum, before 20 weeks of EGA). Women were considered vaccinated if they received the influenza vaccination three months before pregnancy through 19 weeks of EGA (23%, with 20.1% in the 3 months preceding pregnancy and 3% from weeks 4–19 weeks of EGA), and male partners only had baseline vaccination status noted (10.8%). Women in the unvaccinated cohort were similar in all demographic categories to the vaccinated women cohort. In women who received the influenza vaccine, no increased rate of miscarriage was observed if the vaccine was given during the three months before pregnancy (hazard ratio [HR] .99; 95% confidence interval [CI], 0.81–1.20) or if given between 4 and 19 weeks of EGA (HR .83; 95% CI, 0.47–1.47). Similarly, no increase rate of miscarriage was observed in the women of male partners vaccinated during the three months before pregnancy (HR 1.17; 95% CI, 0.73–1.90).This study was limited by secondary analysis of data from another cohort study, a low proportion of Black patients compared with the general population, and a low number of patients with vaccination while pregnant. There were several contextual anomalies which occurred during the study period, such as annual changes to influenza vaccines, appearance of literature which questioned influenza vaccination during pregnancy, and the COVID-19 pandemic. The study concluded that influenza vaccination, either before or during pregnancy, was not linked to an elevated risk of miscarriage.

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 PubMed with the terms [(influenza vaccine[MeSH Terms]) AND (miscarriage[MeSH Terms]) limited to Metanalysis, Randomized Controlled Trial, or Systematic Review] to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: This study underscores that influenza vaccination, either before or during pregnancy, is not linked to an elevated risk of miscarriage. The efficacy of the influenza vaccine during pregnancy has been clearly established. However, a case control study from 2017 called into question the safety of the vaccine with concern for an increased risk of miscarriage despite multiple safety studies before this. Owing to the litigious nature of obstetrical practice, many providers changed their recommendation during early pregnancy due to the 2017 study.

David L. Kriegel, MD
Amy Leurinda, MD
J. Scott Earwood, MD, FAAFP
Department of Family and Community Medicine, Medical College of Georgia at Augusta University, Augusta, GA

The Corresponding Faculty Author on the manuscript is John Earwood; jearwood@augusta.edu
The authors declare no conflict of interest.

Is soft bandaging comparable with rigid immobilization of torus fractures of the wrist in the pediatric population?

Immobilisation of torus fractures of the wrist in children (FORCE): a randomized controlled equivalence trial in the UK

Perry DC, Achten J, Knight R, et al. Immobilisation of torus fractures of the wrist in children (FORCE): a randomised controlled equivalence trial in the UK [published correction appears in Lancet. 2022 Jul 23;400(10348):272]. *Lancet*. 2022;400(10345): 39–47. doi: 10.1016/S0140-6736(2201015-7) doi: 10.1097/EBP.0000000000002043

KEY TAKEAWAY: In children with torus fractures, use of a soft bandage results in similar outcomes as rigid immobilization.

STUDY DESIGN: Randomized, unblinded, controlled equivalence trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFO: A third of individuals sustain a fracture during childhood, and torus fractures of the distal radius are the most common of these fractures. There is common belief that fractures need cast immobilization for both healing and pain control, although prior reviews suggest recovery is similar regardless of treatment (plaster cast, removable splint, or bandage). However, clinical guidelines remain varied because of lack of quality evidence.

PATIENTS: Children with a distal radius torus fracture
INTERVENTION: Soft bandage and immediate discharge
CONTROL: Rigid immobilization and follow-up
OUTCOME: Primary: Pain at three days postrandomization
SECONDARY: Functional recovery, health-related quality of life, analgesia use, days of school or childcare absence, healthcare resource use, complications, satisfaction with treatment

METHODS BRIEF DESCRIPTION:
- A multicenter Forearm Fracture Recovery in Children Evaluation (FORCE) trial conducted at 23 emergency departments in the United Kingdom.
- Children (4–15 years old) with a radiographically confirmed torus fracture of the distal radius were randomized (1:1) to the soft bandage and immediate discharge group versus the rigid immobilization group.
- Exclusion criteria for injuries older than 36 hours, cortical disruption seen on radiograph, and additional fractures outside affected wrist.
- Pain was assessed three days postrandomization using the 0 to 10 point Wong-Baker FACES Pain Rating scale.
- Data were collected at baseline, day 3, day 7, and at three and six weeks.
- Secondary outcomes include functional recovery, health-related quality of life, analgesia use, days of school or childcare absence, healthcare resource use, complications, and satisfaction with treatment measured using various rating scales. These outcomes were proxy (older than 8 years old) or self-reported.
- Self-reported data were collected at six weeks

INTERVENTION (# IN THE GROUP): 489
COMPARISON (# IN THE GROUP): 476
FOLLOW-UP PERIOD: Six weeks

RESULTS:

Primary Outcome:
- The soft bandage group had equivalent pain at three days compared with the rigid immobilization group (3.2 vs 3.1 points; difference –0.09; 95% CI, -0.32 to 0.14).
- No difference in pain at other primary time points including days 0, 1, 7, 21, and 42.

Secondary Outcomes:
- The soft bandage group had a significant increase in the use of analgesia compared with the rigid immobilization group at day 1 (83% vs 78%; OR 0.53; 95% CI, 0.28–0.98), but no difference at any other time points.

LIMITATIONS:
- Inability to mask families likely influenced patient-reported outcomes.
- Exclusions were not made for comorbid diseases which may influence results. EBP

Drew Amador, MD
University of Iowa Family Medicine Residency Program, Iowa City, IA

The corresponding author Drew Amador, MD, drew-amador@uiowa.edu
The author declares no conflicts of interest.

Does Initiating Gender-Affirming Hormone Therapy Treatment in Early Puberty Correlate with Better Mental Health Outcomes?

Psychosocial Functioning in Transgender Youth after 2 Years of Hormones

Chen D, Berona J, Chan YM, et al. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. *New England Journal of Medicine*. 2023; 388(3):240-250. doi:10.1056/nejmoa2206297 doi: 10.1097/EBP.0000000000002155

KEY TAKEAWAY: Initiating gender-affirming hormone therapy (GAHT) in early puberty for transgender and nonbinary youth improves appearance congruence and psychosocial functioning. These improvements correlate to a decrease in anxiety and depression with an increase in psychosocial functioning.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BACKGROUND: Rates of depression, anxiety, and suicide are high among transgender and nonbinary youth when compared with cisgender youth. No previous studies have been performed with a focus on the psychosocial well-being effects of gender-affirming hormone therapy on transgender and nonbinary youth.

PATIENTS: Transgender and nonbinary youth
INTERVENTION: Gender-affirming hormone treatment
CONTROL: No GAHT
OUTCOME: Gender congruence, anxiety, and depression
METHODS BRIEF DESCRIPTION:

- Transgender and nonbinary youth (assigned male at birth [AMAB] and assigned female at birth [AFAB]) between 12 and 20 years old in Tanner stages 2 and 3 who initiated gender-affirming hormone treatment were included in the study.
- Surveys were completed at baseline and 6, 12, 18, and 24 months after GAHT initiation.
- Surveys assessing psychosocial, physical, anxiety, and depression outcomes were utilized:
  - Transgender Congruence Scale which is a 12-item scale that measures the degree to which an individual feels comfortable and genuine in their gender identity and appearance. The higher the score, the higher the congruency.
  - Beck's Depression Inventory-II measures depression utilizing 21 questions. A total score of <10 is normal. Scores greater than 40 indicate extreme depression.
  - Revised Children's Manifest Anxiety scale for 6- to 19-year-old patients is composed of 49 items that comprise 5 scales: physiological anxiety, defensiveness, worry, inconsistent responding, and social anxiety. Norms are separated by different age groups. A T-score greater than 60 indicates a high level of impairment.
  - Positive Affect and Life Satisfaction measures both positive and negative aspects of social and emotional functioning that are considered developmentally relevant at three age ranges (3–7, 8–12, and 13–17 years old). The higher the score, the greater the positive effect and life satisfaction.
- Information was plotted using a latent growth curve to examine initial levels and changes in appearance congruence and how these correlated to each psychosocial outcome.

INTERVENTION (# IN THE GROUP): 315
COMPARISON (# IN THE GROUP): Existing data

FOLLOW UP PERIOD: 24 months

RESULTS:

- GAHT improved appearance congruence compared with no GAHT (annual increase on a 5-point scale, 0.48 points; 95% CI, 0.42–0.54).

- T scores increased for positive affect (annual increase on a 100-point scale, 0.80 points; 95% CI, 0.08–1.54)
- GAHT increased life satisfaction compared with no GAHT (annual increase on a 100-point scale, 2.3 points; 95% CI, 1.6–3.0).
- GAHT reduced depression compared with no GAHT (annual change on a 63-point scale, −1.3 points; 95% CI, −2.0 to −0.57).
- GAHT reduced anxiety compared with no GAHT (annual change on a 100-point scale, −1.5 points; 95% CI, −2.1 to −0.79).

LIMITATIONS:
- A longer length of study would provide more detail on gender incongruence and psychosocial impacts.
- Increasing sample size would increase the power of the data. EBP

Lisa MacVane, MD
University of Massachusetts-Fitchburg Family Medicine, Fitchburg, MA

Corresponding author is Lisa MacVane; lisa.macvane@umass-memorial.org
The author declares no conflict of interest.

Does vitamin D decrease the development of autoimmune disease?

Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial

Hahn J, Cook NR, Alexander EK, et al. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. *BMJ*. 2022; 376:e066452. doi:10.1136/bmj-2021-066452 doi: 10.1097/EBP.0000000000002156

KEY TAKEAWAY: 2000 IU of daily vitamin D decreases the development of autoimmune disorders in older adults by 22%.

STUDY DESIGN: Double blind, randomized, placebo-controlled trial, two-by-two factorial design

LEVEL OF EVIDENCE: STEP 2

BACKGROUND: The prevalence of autoimmune conditions increases each year with no known preventative interventions. Prior animal and human trials of supplementation with vitamin D to reduce autoimmune disease incidence found mixed results. Treatment with omega 3 fatty acids resulted in improved outcomes with some established autoimmune conditions; however, little is known about its ability to prevent these conditions.

PATIENTS: Older adults
INTERVENTION: Vitamin D and omega 3 fatty acid
CONTROL: Placebo
OUTCOME: Autoimmune disease incidence
METHODS BRIEF DESCRIPTION:
- Men ≥50 years and women ≥55 years old living in the United States without hypercalcemia or other serious illness were included in this study.
  - Mean age of the population was 67.1 years.
  - This study included 81% non-Hispanic White, 20% Black, and 9% other racial/ethnic self-identified participants.
- Patients were blinded and randomized to one of the following daily medication regimens:
  - Vitamin D + omega-3
  - Vitamin D + placebo
  - Omega 3 + placebo
  - Placebo + placebo
- Medication regimens included the following:
  - Vitamin D was given as 2000 IU.
  - Omega 3 was given as EPA 460 mg and DHA 380 mg.
  - The matched vitamin D placebo was soybean oil, and the matched omega 3 placebo was olive oil.
- Autoimmune disease incidence was measured by the presence of newly diagnosed rheumatoid arthritis, polymyalgia rheumatica, autoimmune thyroid disease, inflammatory bowel disease, psoriasis, and probable other autoimmune disease as determined by two, blinded physicians specializing in rheumatology, endocrinology, or gastroenterology through chart review.

INTERVENTION (# IN THE GROUP):
- Omega 3 fatty acids + vitamin D: 6,420
- Vitamin D + omega 3 placebo: 6,431
- Omega 3 + vitamin D placebo: 6,432

COMPARISON (# IN THE GROUP): Vitamin D placebo + omega 3 fatty acid placebo: 6,441

FOLLOW-UP PERIOD: Five years

RESULTS:

PRIMARY OUTCOME:

- Vitamin D supplementation reduced the incidence of autoimmune disease at 5 years compared with placebo (hazard ratio [HR] 0.78; 95% CI, 0.61–0.99).
- Omega 3 fatty acid supplementation failed to decrease autoimmune disease incidence at 5 years compared with placebo (HR 0.85; 95% CI, 0.67–1.1).
- With exclusion of the first two years of follow-up:
  - Taking vitamin D resulted in significantly less autoimmune disease occurrence compared with placebo (HR 0.61; 95% CI, 0.43–0.86).
  - Omega 3 fatty acid supplementation created no significant effect on autoimmune development (HR 0.90; 95% CI, 0.64–1.3).

LIMITATIONS:

- Data cannot be extrapolated to younger age groups.
- The minimal effective dose of vitamin D cannot be determined.
- Shorter follow-up duration may have resulted in missing new onset of autoimmune diseases. EBP

David Lee Rebedew, MD
Mercyhealth Family Medicine Residency Program - Janesville, Janesville, WI

The corresponding author is David Lee Rebedew; drebedew@mhemail.org

The author declares no conflicts of interest.

In patients with presumed adhesive small bowel obstruction, does management with a water-soluble contrast protocol improve outcomes compared with usual care?

EVIDENCE-BASED ANSWER

Managing adhesive small bowel obstructions with water-soluble contrast protocols does not decrease operative rates but decreases hospital length of stay by approximately 2 days without increasing complications (SOR: **A**, meta-analyses of randomized controlled trials).

doi 10.1097/EBP.0000000000002177

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

A 2022 systematic review of 11 randomized controlled trials (RCTs; N=817) and nine cohort studies (N=3,944) investigated the efficacy of water-soluble contrast (WSC) administered by nasogastric tube in the management of adhesive small bowel obstruction.[1] Researchers included studies examining the effect of WSC on operative rates or hospital length of stay (LOS) compared with nasogastric suction alone with or without placebo saline or water. The studies included patients with radiographically confirmed small bowel obstruction presumed secondary to adhesions and excluded patients with an acute abdomen, recent abdominal surgery (within 6 weeks), or a nonadhesive cause of obstruction. WSC was given on admission or up to 68 hours later, and follow-up films (on WSC patients only) were obtained from 2 to 72 hours after WSC administration. Although not described, the authors stated most trials used a protocol to determine surgical intervention based on the follow-up films; only a few of the trials reported hospital discharge criteria. In pooled analysis of only the RCTs, no difference was noted in operative rates between those managed with WSC and control patients (10 trials, N=829; risk ratio [RR] 0.90; 95% CI, 0.53–1.6). In comparison, those managed with WSC had a shorter LOS by 1.95 days (10 trials, N=829; 95% CI, 0.56–3.3). Overall complications (not defined) and mortality did not differ between groups. No complications that could be directly linked to WSC (hypovolemia, electrolyte imbalance, or allergic reactions) were reported in the eight RCTs and three cohort studies evaluating this. The authors noted some of the included studies were limited by lack of protocols for use of post-WSC imaging (4 trials), lack of criteria for surgical intervention (2 trials) and hospital discharge (7 trials), and lack of double blinding (10 trials).

A 2015 RCT (n=242) was the largest trial in the meta-analysis above and contributed significantly to the results.[2] This RCT included adult patients presenting with an uncomplicated small bowel obstruction thought to be secondary to adhesions confirmed by computed tomography (CT). Researchers excluded patients with other causes of obstruction or surgery within the previous four weeks. After two hours of nasogastric suctioning, patients were randomized to 100 mL WSC by nasogastric tube or 100 mL saline solution placebo. Patients administered WSC had abdominal radiographs at 8, 12, 24, and 48 hours. If they did not pass flatus or if contrast did not appear in the colon within 48 hours, they were taken to surgery. In the saline group, patients were taken to surgery if they did not pass flatus in 48 hours. All patients had surgical intervention for signs of peritonitis. The primary outcome of operative rates did not differ between the groups, 24% in the WSC group versus 20% in the saline group (odds ratio [OR] 1.3; 95% CI, 0.69–2.4). Similarly, no difference was noted in the secondary outcome of LOS, 3.8 days with WSC and 3.5 days with saline (P=.19). The authors also included a systematic review and meta-analysis in this report evaluating 10 English-language RCTs (N=748) of patients with radiographically confirmed small bowel obstruction presumed secondary to adhesions, which they then pooled with their own trial. Of note, eight of these RCTs were also included in the 2022 systematic review above. Further study inclusion and exclusion criteria were not reported. Regarding pooled analysis of operative rates in the older RCTs, results favored WSC versus control (9 trials, N=748; OR 0.62; 95% CI, 0.44–0.87). However, when the present trial was included, the difference became nonsignificant (10 trials, N=990; OR 0.69; 95% CI, 0.47–1.01). Similarly, for LOS in the older RCTs, WSC managed patients had a shorter stay compared with control (6 trials, N=558; mean difference [MD] –2.2 days; 95% CI, –2.6 to –1.7). This difference disappeared when this trial was included (7 trials, N=800; MD = –0.02; 95% CI, –0.18 to 0.13). Of note, assessing operative rates at 48 hours may have missed some operative interventions occurring later during the hospitalization. In addition, even though published in 2017, the study was completed from 2006 to 2009. The reasons for delayed publication were not reported. EBP

Luke McFarland, DO
Thomas Satre, MD
University of Minnesota / CentraCare St. Cloud Family Medicine Residency, St. Cloud, MN

The corresponding author is Thomas Satre; satret@centracare.com
The authors declare no conflicts of interest.

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Is HbA1c an appropriate diagnostic tool for gestational diabetes?

EVIDENCE-BASED ANSWER

The HbA1c test may be useful diagnosing gestational diabetes mellitus (GDM) in the second or third trimester with a cut-off of 5.7% (SOR: **A**, meta-analysis of cohort studies). The HbA1c test has a high specificity to diagnose GDM when an HbA1c threshold of 5.8% is used (SOR: **B**, meta-analysis of cohort studies).

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

In 2020, a meta-analysis of 23 prospective and retrospective cohort studies (N=16,921) evaluated the accuracy of the HbA1c as a screening and diagnostic test for gestational diabetes mellitus (GDM).[1] The review included studies of pregnant women with and without risk factors for GDM who underwent testing of with an HbA1c and an oral glucose tolerance test (OGTT). Risk factors included body mass index above 30 kg/m^2, previous macrosomic baby, previous GDM, family history of diabetes, and minority ethnic family origin with a high prevalence of diabetes. It also included studies where HbA1c testing was done in the first trimester with OGTT in the second or third trimester. In pregnant women with risk factors for GDM, the optimal sensitivity of HbA1c to diagnose GDM was a cutoff of 5% (17 studies, N=8,067; sensitivity 0.88 and specificity 0.26, with positive likelihood ratio [+LR] of 1.2 and negative likelihood ratio [–LR] of 0.49). In pregnant women without risk factors for GDM, the optimal HbA1c cutoff to diagnose GDM was 5.2% (6 studies, N=8,854; sensitivity 0.86 and specificity 0.32, with +LR 1.3 and –LR 0.43). In all pregnant women who underwent HbA1c testing during the second or third trimester and optimizing sensitivity, the HbA1c cutoff to diagnose GDM was 5.1% (17 studies, N=9,821; sensitivity 0.82, specificity 0.40, +LR 1.4, and –LR 0.45). If optimizing specificity, the HbA1c cutoff to diagnose GDM was 5.7% (17 studies, N=9,821; sensitivity 0.36, specificity 0.90; +LR 3.6; and –LR 0.71). Two studies were rated as high risk of bias because of the interpretation and reporting of the reference standard test criteria and unclear sampling method. Heterogeneity was noted because of population groups sampled, the trimester in which HbA1c testing was performed, and the diagnostic criteria for OGTT.

In 2020, a meta-analysis of 19 prospective and retrospective cohort studies (N=32,669 pregnancies) evaluated the diagnostic accuracy of HbA1c for GDM.[2] It evaluated pregnant patients in any trimester of pregnancy for GDM through a simultaneous or interval reference standard two-hour 75 g OGTT and an index HbA1c test. Ten cohort studies overlap with the prior meta-analysis. A range of HbA1c cutoff values from 4.5 to 6.0% were analyzed. The primary outcome was the diagnostic accuracy of HbA1c for gestational diabetes. At 4.6% HbA1c, the sensitivity was maximized (4 trials, N=23,018; sensitivity 0.91, specificity 0.2, +LR 1.2, and –LR 0.43). Optimizing specificity, the HbA1c cutoff was 5.8% (4 trials, N=4,222; sensitivity 0.073, specificity 0.99, +LR 8.4, and –LR 0.94). At an HbA1c threshold of 5.0%, the sensitivity and specificity were equivalent at 0.62 (5 trials, N=23,547). A major limitation of the analysis was the different timing of gestational age during administration of the OGTT and HbA1c and lack of risk stratification between high-risk and low-risk groups. EBP

Spencer Lindsay, MD
Patrick Mitchell, DO
Sarah Daly, DO FAAFP
Utah Valley Family Medicine Residency, Provo, UT

The corresponding author is Sarah Daly; sarah.daly@imail.org.
The authors declare no conflicts of interest.

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Is exercise therapy effective for low back/pelvic pain in pregnant patients in the second or third trimester?

EVIDENCE-BASED ANSWER

Probably. Exercise programs improve pregnancy-associated low back pain but do not consistently prevent or improve pelvic pain (SOR: **B**, meta-analyses and systematic reviews of randomized controlled trials [RCTs]). However, pregnant patients who participate in exercise programs are less likely to have new episodes of sick leave because of their low back or lumbopelvic pain, suggesting a nonquantifiable component to the benefits of exercise (SOR: **B**, meta-analyses and systematic reviews of RCTs).

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

A 2015 Cochrane systematic review of 34 randomized controlled trials (RCTs; N=5,121) compared usual prenatal care to any intervention to prevent or reduce the incidence or severity of pelvic pain, low back pain (LBP), both, related functional disability, or sick leave.[1] This review included trials with pregnant women 16 to 45 years old and between 12 to 38 weeks' gestation. The interventions included exercises (land or water based), pelvic belts, osteopathic manipulative therapy, spinal manipulative therapy, neuro-emotional technique, craniosacral therapy, transcutaneous electrical nerve stimulation, kinesio-taping, yoga, acupuncture, and multimodal approaches. Interventions were added to usual prenatal care and compared with the standard prenatal care alone. Primary outcomes were pain intensity (visual analogue scale [VAS] or mean difference [MD]; lower scores=better), back- or pelvic-related functional disability or functional status (Roland Morris Disability Questionnaire or Oswestry Disability index; lower score=‴ better), days off work or sick leave or adverse effects as defined by the trialist. Low-quality evidence noted that group exercise with education was not better at preventing LBP than usual prenatal care (2 trials; N=374; risk ratio [RR] 0.97; 95% CI, 0.80–1.2). Moderate-quality evidence suggested a reduction in low back and pelvic pain on a VAS scale for those who participated in an 8- to 12-week exercise program (4 trials; N=1,176; RR 0.66; 95% CI, 0.45–0.97). Land-based exercise was found to reduce sick leave related to low back pain and pelvic pain (2 trials; N=1,062; RR 0.76; 95% CI, 0.62–0.94). Meta-analysis and subgroup analysis could not be done in some studies because of heterogeneity between individual trials. The overall risk of bias was deemed high.

A 2018 meta-analysis of 11 RCTs (N=2,347) investigated the effects of exercise interventions compared with usual daily activities in the prevention or reduction of pelvic pain, low back pain, lumbopelvic pain, and related sick leave.[2] This analysis included trials with pregnant women with and without baseline pain that were either healthy, obese, or sedentary. Gestational age ranged from 12 to 30 weeks. The duration of the interventions ranged from seven to 20 weeks, and follow-up varied between two to eight months. The exercise interventions included water gymnastics, pelvic tilt exercise, energy expenditure exercise, strengthening exercises, low impact gymnastics with strengthening exercises, or a combination of at least three of aerobic, strengthening, stretching/relaxation, flexibility, endurance, resistance, pelvic floor muscle training, or balance exercises. Meta-analysis of seven RCTs found that exercise reduced the risk of low back pain in pregnancy by 9% (N=1,175; RR=0.91; 95% CI, 0.83–0.99) and prevented new episodes of sick leave secondary to low back pain (2 trials; N=349; RR=0.67; CI, 0.40–1.12) or lumbopelvic pain (3 trials; N=1,168; RR=0.79; CI, 0.64–0.99). No protective effect of exercise against pelvic pain (4 trials; N=565; RR=0.99; CI, 0.81–1.21) or lumbopelvic pain (8 trials; N=1,737; RR=0.96; 95% CI, 0.90–1.02) was noted. The reported observed heterogeneity for this analysis was low; however, the authors noted differences in individual interventions' nature, timing, frequency, and duration. No evidence of publication bias was noted. EBP

Sarah Torres, MD
Susana Peralta, DO
Roberto Silva, MD
University of Colorado Family Medicine Residency, Denver, CO

The corresponding author is Roxanne Radi, MD; Roxanne.radi@dhha.org

The authors declare no conflicts of interest.

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In patients with type II diabetes mellitus, is gabapentin or an SNRI more effective at treating symptoms of diabetic neuropathy?

EVIDENCE-BASED ANSWER

No difference was noted between duloxetine or gabapentin for symptom improvement in painful diabetic neuropathy, but less adverse events are noted with duloxetine (SOR: **B**, meta-analysis of randomized clinical trials with limitations). Both serotonin and norepinephrine reuptake inhibitor and gabapentin are recommended first-line therapies (SOR: **B**, evidence-based guideline).

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

In 2022, a meta-analysis of seven randomized clinical trials (RCTs; N=624) compared the efficacy and safety of duloxetine and gabapentin in the treatment of diabetic peripheral neuropathic pain.[1] The study included adult patients with type two diabetes and peripheral neuropathy with a minimum pain score of 40 points on a 100-point visual analog pain scale (VAS). Exclusion criteria were patients with alcoholism, cognitive impairment, or drug use. Patients received 60 to 120 mg of duloxetine daily or a total of 900 to 3,600 mg of gabapentin daily for 4 to 12 weeks. The primary outcomes were pain as measured on the VAS and the incidence of adverse reactions. Secondary outcomes included response rate, sleep interference score, and clinical global impression of change. No difference was noted in VAS pain scores between the duloxetine and gabapentin groups (7 trials, N=624; standardized mean difference [SMD] −0.14; 95% CI, −0.31 to 0.03; I^2=0%). A lower incidence of adverse effects was noted with duloxetine compared with gabapentin (6 studies, N=538; risk ratio 0.59; 95% CI, 0.45–0.79). No difference was noted in the response rate or clinical global impression of change. A small improvement was noted in the sleep interference score in the duloxetine group over the gabapentin group (2 studies, N=204; SMD –0.35; 95% CI, −0.63 to−0.08). No specific side effects were noted in this meta-analysis but one of the open-label RCTs noted that nausea and vomiting appeared to be the most common side effects of both duloxetine and gabapentin. Limitations of this review included a small sample size as well limited ethnic diversity. No descriptions of how the response rate, clinical global impression of change, or sleep interference outcomes were measured. In addition, funnel plot analysis revealed a possible publication bias.

In 2022, the American Academy of Neurology issued an evidence-based practice guideline on oral and topical treatment of painful diabetic polyneuropathy for clinicians, based on its own literature review.[2] The guideline stated that clinicians should offer tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitor (SNRI), gabapentinoids, or sodium channel blockers to reduce pain (level B, strong recommendation based on moderate confidence in inference and evidence). A moderate reduction of pain was noted compared with placebo with gabapentin (1 trial, n=not provided; SMD 0.53; 95% CI, 0.22–0.84) and SNRIs (9 trials, N=not provided; SMD 0.47; 95% CI, 0.34–0.60). Furthermore, the guidelines recommend that clinicians should consider factors other than efficacy, including potential adverse effects, patient comorbidities, cost, and patient preferences, when recommending treatment (level B—strong recommendation based on moderate confidence in inference and evidence). A majority (82%) of the members on the guideline expert panel were free from conflicts of interest. Three of the guideline developers were determined to have conflicts of interest and were thus not permitted to review or rate the evidence, but they did serve in an advisory capacity on other aspects of the guidelines. EBP

Brett Jackson, MD
Jordan Rawlings, DO
Sarah Daly, DO FAAFP
Utah Valley Family Medicine Residency, Provo, UT

The corresponding author is Sarah Daly; sarah.daly@imail.org.
The authors declare no conflicts of interest.

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In patients with advanced chronic kidney disease (stage IV or V), does the continued use of renin–angiotensin system inhibitors have a worsening effect on renal function?

EVIDENCE-BASED ANSWER

No. The continued use of renin–angiotensin system inhibitors is unlikely to have a worsening effect on renal function in advanced chronic kidney disease (stage IV or V; SOR: **B**, consistent results across 2 RCTs and 1 cohort study).

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

A 2001 post hoc analysis of a randomized controlled trial (n=322) compared the rate of glomerular filtration rate (GFR) change and incidence of end-stage kidney disease (ESKD) in adult patients with nondiabetic chronic nephropathies when initiated on angiotensin-converting enzyme (ACE) inhibitor therapy versus standard non-ACE inhibitor antihypertensives at escalating doses to achieve blood pressure control defined as a diastolic blood pressure <90 mmHg.[1] Patients were 18 to 70 years old, mostly male, and patients with diabetes were excluded. The patients' GFR was monitored (by iohexol clearance) at standardized regular intervals over five years. Patients were categorized into three groups (tertiles) based on basal estimated glomerular filtration rate (eGFR). The lowest tertile group had a mean eGFR of 25 mL/min/1.73 m^2, corresponding to chronic kidney disease stage IV and V. The study found similar rates of eGFR decline in all three tertile groups (22%, 22%, and 35% grouped from lowest basal eGFR to highest basal eGFR [$P<.05$]). However, ACE inhibitor therapy produced a decrease in the incidence of ESKD by 33% ($P<.05$), 37%, and 100% ($P<.01$), respectively, in the three tertiles. Adverse events were also comparable among the three groups and across interventions. The study was of good quality, although somewhat limited because of age of article (2001) and lack of inclusion of patients with diabetic nephropathy.

A 2022, multicenter open-label RCT (n=411) compared the continuation of renin–angiotensin system (RAS) inhibitors and discontinuation of RAS inhibitors in adults with eGFRs <30 mL/min/1.73 m^2 not receiving dialysis and who had not undergone kidney transplantation.[2] Patients had a median age of 63 years old, with 37% diagnosed with diabetes and 85% White. The primary outcome was eGFR at three years, and secondary outcomes included hospitalization, cardiovascular events, death, and time until the development of ESKD defined as reduction of eGFR by 50% or initiation of renal replacement therapy. Follow-up of all patients took place every three months for three years after randomization. The study found no significant difference in the eGFR change between the continuation and discontinuation groups (difference, –0.7 mL/min/1.73 m^2; 95% CI, –2.5 to 1.0), with a negative value favoring the outcome in the continuation group. The study was of moderate quality although the open-label nature of the trial could have affected clinical care and subjective endpoints.

A 2020 propensity-matched cohort study (n=678) compared the progression of ESKD and all-cause mortality among patients with an eGFR <30 mL/min/1.73 m^2 with varying degrees of RAS inhibitor use.[3] Patients had an average age of 59 years old, and 54% had diabetes. A single physician categorized patients use of RAS inhibitors as never users, dynamic users (on and off users), new users, and always users. The study demonstrated no significant difference in progression to ESKD among all four patterns of use compared with the always users reference group: never users (hazard ratio [HR] 1.09; 95% CI, 0.71–1.67), dynamic users (HR 1.46; 95% CI, 0.83–2.55), and new users (HR 0.78; 95% CI, 0.33–1.84). Similarly, researchers found no significant difference in all-cause mortality among the different patterns of use compared with always users: never users (HR 1.02; 95% CI, 0.74–1.40), dynamic users (HR 1.23; 95% CI, 0.80–1.90), and new users (HR 1.10; 95% CI, 0.63–1.92). One limitation of the study was that patients were only contacted every six months. EBP

Justin Chen, DO
Chukwuemeka Enwezor, MD
Adesina Adedeji, MD
Swedish Hospital Family Medicine Residency, Chicago, IL

The corresponding author is Justin Chen; jchen@schosp.org
The authors declare no conflicts of interest.

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Is ashwagandha effective at reducing anxiety symptoms in adults?

EVIDENCE-BASED ANSWER

Daily ashwagandha root extract supplementation may reduce anxiety symptoms by as much as 24% compared with placebo (SOR: **C**, meta-analysis of low-quality randomized controlled trials [RCTs] with significant heterogeneity and recent small RCT).

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

A 2022 meta-analysis (12 randomized controlled trials [RCTs], N=1,002) evaluated the effect of ashwagandha root extract on anxiety and stress.[1] Patients included healthy adults (25–48 years old) with a history of generalized anxiety disorder, insomnia, schizoaffective or schizophrenic disorder, or bipolar disorder. Researchers excluded pregnant and lactating women. The studied intervention was daily supplementation with ashwagandha root extract. Ashwagandha is a plant native to India and the Middle East believed to have a calming effect within traditional Indian medicine. Dosages generally ranged from 250 to 1,000 mg daily, with one study using a dose of 12,000 mg daily. Duration of treatment ranged from eight to 12 weeks. All studies used matching placebo for comparison. The primary outcome was change from baseline posttreatment in anxiety symptom scores evaluated by various scales including Hamilton Anxiety Rating Scale (HAM-A), modified HAM-A, Depression Anxiety Stress Scale (DASS), or Perceived Stress Scale (PSS). The overall effect was pooled across various scales by random-effects model and the standardized mean difference (SMD) was calculated (SMD >0.8 indicates a large effect compared with placebo). Daily ashwagandha root extract supplementation reduced anxiety symptoms compared with placebo (9 RCTs, N=540; SMD 1.6; 95% CI, 0.74–2.4). Significant heterogeneity was reported (I^2=93.8%), so subgroup analysis for different patient ages and doses was performed. The groups found to have the greatest benefit were patients 40 years old or older (SMD 2.1; 95% CI, 3.1–0.96) and ashwagandha doses of 600 mg or more daily (SMD 2.30; 95% CI, 3.5–1.1). Adverse effects were not reported. Limitations included small study sizes and significant variation among included patient diagnoses, ashwagandha doses, and outcome assessment scales.

A 2023 double-blinded, placebo-controlled RCT (n=54) evaluated the effectiveness of ashwagandha root extract on reducing stress and anxiety in adults.[2] Researchers included adult patients (21–54 years old) with Perceived Stress Scale (PSS; range 0–40) scores between 14 and 25 (defined as moderate anxiety) and Generalized Anxiety Disorder 7-Item (GAD-7; range 0–21) scores less than 15 (defined as mild-to-moderate). Exclusion criteria included a history of any other psychological condition or chronic medical condition, pregnant or lactating women or use of herbal or alternative therapies within the last month. The intervention group received a daily capsule of ashwagandha root extract at a dose of 500 mg, whereas the control group received a similar placebo capsule daily. The primary outcome was change in PSS and GAD-7 scores from baseline after 60 days of treatment. Compared with placebo, patients who took ashwagandha root extract had a 24% larger reduction in both PSS (mean difference [MD] 9.7; 95% CI, 7.6–12) and GAD-7 scores (MD 5.1; 95% CI, 3.5–6.7) after 60 days of treatment. Researchers reported 30% (8/27) of treatment group participants had "mild transient discomfort" that resolved within 24 hours. Limitations of this review included small sample size, predominantly male participants, and short-term follow-up. EBP

Sarah Ericson, DO
Kara Babo, MD, CAQSM
David Grant Medical Center Family Medicine Residency Program, Travis AFB, CA

The corresponding author is Kara Babo; kbabo37@gmail.com
The authors declare no conflicts of interest.
The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the U.S. Air Force Medical Department, the Air Force at large, or the Department of Defense.

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In patients who endorse heavy cannabis use, is there an increased risk for lung cancer?

EVIDENCE-BASED ANSWER

When controlling for tobacco exposure, cannabis use of any amount is not associated with an increased risk of lung cancer (SOR: **B**, 2 meta-analyses of cohort studies).

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

A 2015 pooled analysis of six case–control studies (N=5,144) evaluated the association between cannabis use and the risk of developing lung cancer.[1] The pooled studies included adults with lung cancer (N=2,156) and healthy controls (N=2,985) from the United States, Canada, the United Kingdom, and New Zealand. The median patient age across all studies was 53 years old for controls and 57 years old for cases. Cases were further subdivided between habitual and nonhabitual users, defined as those with at least one joint-year of exposure (365 joints per year) and those with less than one joint-year of exposure. Some studies also included a category for continuous users, defined as those with greater than 20 years of cannabis exposure. All studies completed subgroup analyses for sex and tobacco smoking status. The primary outcome was the occurrence of any histologically confirmed lung carcinoma, including adenocarcinoma, squamous cell carcinoma, and small cell lung cancer. The quality of evidence overall was determined to be moderate. Compared with nonhabitual or never users, no difference was noted in the number of lung cancer cases for habitual users (odds ratio [OR] 0.88; 95% CI, 0.63–1.2). No difference was also noted between continuous cannabis smokers and nonusers (OR 0.99; 95% CI, 0.97–1). Limitations included the strong correlation between cannabis and tobacco use among cases confounding some data, differences in cannabis exposure inherent in different strengths of cannabis products, interstudy heterogeneity related to regional differences in cannabis use, and recall bias associated with questionnaire formats.

A 2019 systematic review and meta-analysis evaluated the association between cannabis smoking and the risk of multiple cancers including lung cancer.[2] Eight studies in the analysis looked specifically at lung cancer (N=146,221). The studies from the pooled analysis above was included in this meta-analysis, but the majority of patients were from two cohort studies from 2013 and 1997. All studies were cohorts (1 prospective, 1 retrospective, and 1 cross-sectional) or case–control studies. The majority of patients included were from North America or Sweden, and all studies included adult patients who endorsed at least one joint-year of cannabis exposure. Lung cancer data were not amenable to pooled analysis. Results were mixed across the studies, and all studies were at moderate or high risk of bias, primarily because of recall and not controlling for cigarette smoking. The authors determined that the data were insufficient to determine an association between cannabis use and lung cancer. Limitations included multiple studies that did not control for tobacco use, some studies that included mixed cannabis and tobacco use, short follow-up periods, or limited data on continued exposure. EBP

David Moss, MD, FAAFP
Aaron Griffin, MD
Nellis Air Force Base Family Medicine Residency, Las Vegas, NV

The corresponding author is David Moss; david.a.moss42.civ@health.mil.
The authors declare no conflicts of interest.
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Do opioid antagonists (naltrexone) lead to better tobacco cessation compared with placebo?

EVIDENCE-BASED ANSWER

No. When naltrexone is compared with placebo, it does not increase the proportion of people who stop smoking, either at the end of treatment or at six months or more after treatment (SOR: **A**, systemic review and meta-analysis of randomized control trials [RCTs]). Naltrexone does not improve smoking cessation rates among heavy alcohol drinkers (SOR: **B**, RCT).

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

In 2013, a systematic review and meta-analysis of eight randomized control trials (RCTs) (N=1,213) evaluated the efficacy of naltrexone alone or as an adjunct to nicotine replacement therapy (NRT) for smoking cessation.[1] Patients were adults predominantly from the United States; one trial (n=65) was located in Brazil. Two trials (N=144) enrolled patients with alcohol dependence or significant mental illnesses (eg, major depression with psychosis, schizophrenia or schizoaffective disorder, bipolar disorder). The naltrexone dose varied from 25 mg to 100 mg PO daily, with most trials using 50 mg per day. Treatment duration ranged from four to 27 weeks (median and average duration 12 weeks). Trials used naltrexone with NRT (4 RCTs, N=768) and without NRT (5 RCTs, N=445). The comparator was placebo, with or without NRT (as appropriate per the intervention), in all trials. The primary outcome was abstinence at longest follow-up, and abstinence at end of treatment was a secondary outcome. Researchers assessed long-term smoking cessation using patient self-reports, and six trials (N=1,069) verified abstinence by checking plasma cotinine or breath carbon monoxide levels. Follow-up was three months (1 RCT, n=79), six months (5 RCTs, N=527), and 12 months (2 RCTs, N=607). Naltrexone provided no significant improvement in smoking abstinence at longest follow-up when compared with placebo (8 RCTs, N=1,213; relative risk [RR] 0.97; 95% CI, 0.76–1.2). In subgroup analyses, naltrexone was not more effective than placebo, neither when combined with NRT (4 RCTs, N=768; RR 0.95; 95% CI, 0.70–1.3) nor when used alone (5 RCTs, N=445; RR 1.0; 95% CI, 0.66–1.5). No significant differences were observed between naltrexone and placebo, either with or without NRT, in abstinence at end of treatment. Most studies were deemed to be low risk of bias, but three studies lacked detailed information on methodology, and two studies reported drop-out rates greater than 30%.

A 2017 RCT (n=150) examined the efficacy of naltrexone among heavy alcohol drinkers seeking smoking cessation treatment.[2] Patients were from Rhode Island, had a mean age of 42 years old, and smoked an average of nine cigarettes per day for one or more years; 59% were male, and 28% met criteria for alcohol dependence. To be included, patients had to report drinking heavily at least once (on average) per month (defined as ≥4 drinks per occasion for women and ≥5 drinks for men) and indicate that they were not using other tobacco products or nicotine replacement therapy. On average, patients reported consuming 25 drinks per week and drank heavily 26% of the time. The study excluded patients with substance dependence (other than nicotine and alcohol), significant mental illnesses (eg, major depression or mania, psychosis), abnormal liver enzymes (≥3 times upper limit of normal), or current pregnancy or lactation. Patients in the intervention group received oral naltrexone 50 mg daily starting two weeks before the target quit smoking date and then continuing 50 mg daily for a total of 10 weeks. The control group received placebo, and both groups received a concomitant six-week course of transdermal nicotine patches and six individual counseling sessions over nine weeks that addressed both heavy drinking and smoking. A primary outcome was the seven-day point prevalence of self-reported smoking abstinence measured over 26 weeks after the quit smoking date, verified with breath carbon monoxide levels. A secondary outcome was continuous smoking abstinence, defined as no smoking from 2 to 26 weeks. Naltrexone compared with placebo did not affect smoking abstinence rates over 26 weeks (odds ratio 0.93; 95% CI, 0.46–1.9) nor continuous smoking abstinence from 2 to 26 weeks. This RCT was limited by suboptimal compliance with treatments (<75% took medications when assessed by pill count), by not using biochemical verification of naltrexone compliance, and by a lower-than-anticipated enrollment which diminished the statistical power. EBP

Joel David Alvarez, MD
Enrique Leon, MD
Tacoma Family Medicine, Tacoma, WA

The corresponding author is Enrique Leon; enrique.leon@multi-care.org.
The authors declare no conflicts of interest.

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In patients with chronic low back pain, does sensory training reduce pain intensity?

EVIDENCE-BASED ANSWER

In patients with chronic low back pain, sensory training is no more effective than control therapy for pain relief (SOR: **B**, meta-analysis of mostly small randomized controlled trials [RCTs]). Less than a 1-point difference on a 10-point scale is noted when comparing sensory discrimination acupuncture with usual acupuncture (SOR: **C**, small randomized crossover study). No difference is noted between multimodal therapy compared with usual physiotherapy (SOR: **C**, small RCT).

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

A 2020 systemic review evaluated 10 randomized controlled trials (RCTs; N=350) comparing the efficacy and safety of sensory discrimination training (SDT), a form of feedback-guided sensory training, in the treatment of chronic musculoskeletal pain versus control.[1] Seven of the RCTs specifically focused on the efficacy of SDT in chronic low back pain (CLBP). The review included studies of adults with chronic pain, defined as pain without apparent biological value that had persisted beyond the normal tissue healing time, usually taken to be three months. The intervention was SDT (this included electrical pulse stimulation, perceptive pulse stimulation, and manual/tactile stimulation methods) versus no treatment, usual care, or placebo. The follow-up period was anywhere from two weeks to six months. The primary outcome measured was improvement in pain score documented using a visual analog sale or a numerical rate scale. The secondary outcomes were health, well-being, physical function, sensorimotor function, quality of life, and patient satisfaction. Data were not pooled because of high heterogeneity between the trials. Overall, of the seven RCTs included for CLBP, only one favored SDT over the control group for pain improvement using a 10-point scale (mean difference [MD] 3.0; 95% CI, 1.9–4.1). The other six RCTs did not show a statistically significant difference between SDT and control versus sham treatment on pain intensity in the immediate to medium term for patients with CLBP. The authors mentioned that given the disparity of the data, no clear conclusions regarding secondary outcomes were noted. Study was limited by the quality of evidence that was downgraded to very low quality because of problems with inconsistency, imprecision, and indirectness.

A 2013 randomized crossover experiment compared acupuncture with sensory discrimination training to usual acupuncture (n=25).[2] The trial included patients who were 18 to 60 years old with nonspecific low back pain for a minimum of six months and who rated their low back pain as at least moderate on a provided questionnaire. The study documented efficacy with a 0 to 10 pain scale immediately after performance of 10 repeated lumbar spine active movements. This study revealed the average pain intensity was less with sensory discrimination acupuncture than usual acupuncture (MD –0.8; CI, –1.4 to –0.3). Of note, the study showed that pain was less after both treatments regardless of the order in which usual acupuncture or acupuncture with SDT was used (MD –0.9; CI, –0.3 to –1.5). Key weaknesses included inability to blind participants to treatment, use of self-reported outcomes, short follow-up, and small size.

In a 2015 single-center, assessor blinded randomized controlled trial, which compared the short-term effect of multimodal treatment (neurophysiological education and sensorimotor retraining; n=14) to usual physiotherapy (n=14) in the short-term effect on pain and function in patients with chronic or recurrent nonspecific low back pain.[3] The trial included men and women 18 to 60 years old with a history of three or more months of low back pain, at least moderate disability, and medium or high risk of poor outcome. Patients were followed for 12 weeks after establishing a baseline before initial treatment. The primary outcome measured was mean pain intensity over the prior seven days evaluated with a numerical rating scale (0–10), which showed the effect was smaller than the minimally clinical important difference of 1.7 (MD 1.45; 95% CI, 0.0–4.0). EBP

Elissa Palmer, MD, FAAFP
Sabrina Colombini, MD
Gursharan Narwal, MD
Family Medicine Residency Program, Kirk Kerkorian School of Medicine, UNLV, Las Vegas, NV

The corresponding author is Elissa Palmer; elissa.palmer@unlv.edu
The authors disclose no conflicts of interest.

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How effective is the bivalent prefusion F vaccine versus the RSV preF protein vaccine in preventing RSV in older adults?

EVIDENCE-BASED ANSWER

Both respiratory syncytial virus vaccines are similarly efficacious at six months, although long-term data are lacking to evaluate superiority (SOR: **A**, consistent results from 2 large randomized controlled trials [RCTs]). Neither vaccine produces significant adverse vaccine-related outcomes (SOR: **A**, consistent results from 2 large RCTs).

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

A 2023 phase 3 international randomized controlled trial (RCT; n=24,966) evaluated the vaccine efficacy of one dose of the respiratory syncytial virus (RSV) PreF3 Older Adult (OA) vaccine against RSV-related lower respiratory tract disease during one RSV season.[1] Participants were at least 60 years old who were medically stable (chronic stable medical conditions with or without specific treatment) and with no history of being enrolled in an RSV vaccine trial. Individuals with serious/unstable chronic illnesses or immunosuppressive or immunodeficient conditions were excluded. Participants were randomly assigned in a 1:1 ratio to receive the RSVPreF3 OA vaccine or placebo and were followed starting from the day of injection to six months. The intensity of adverse events was graded by participants for solicited events and by investigators for unsolicited events, ranking from mild (grade 1) to severe (grade 3). After comparing the placebo versus vaccinated individuals for six months, the vaccine was shown to be 83% effective (95% CI, 58–94%) against reverse-transcriptase polymerase chain reaction–confirmed RSV infections and a 94% (95% CI, 62–99%) against severe RSV-related lower respiratory tract disease. Investigators found no difference between vaccine or placebo groups for serious adverse events. Solicited events, primarily injection-site pain, was seen in 61% in the vaccine group and 9% in the placebo group. The most common systemic adverse event was fatigue in both the vaccine group (34%) and the placebo group (16%).

Another 2023 double-blind, placebo-controlled, proof-of-concept trial phase 2 (n=5,782) evaluated the efficacy, immunogenicity, and safety of an Ad26.RSV.preF–RSV preF protein vaccine during one RSV season (Supplementary Appendix http://links.lww.com/FPIN/A366).[2] Participants were 65 years or older and were medically stable with a BMI less than 40 kg/m^2. A small subgroup (n=1,408) with increased risk of severe RSV-mediated lower respiratory tract disease (at risk or with chronic cardiac/pulmonary/kidney disease or diabetes) was also identified. Individuals with severe or potentially life-threatening chronic disorders, such as severe chronic cardiac or lung disease, end-stage renal disease, and Alzheimer disease were excluded. Participants were randomly assigned in a 1:1 ratio to receive the Ad26.RSV.preF–RSV preF protein or placebo. All participants were followed starting from the day of injection to six months or until the end of the RSV season, whichever occurred later. The primary endpoint of the study began after the first occurrence of RSV-mediated lower respiratory tract disease meeting one of three set case definitions. Definition 1 consisted of three or more lower respiratory tract infection (RTI) symptoms; definition 2 group had two or more lower RTI symptoms; and definition 3 participants had one or more lower RTI symptoms along with at least one systemic symptom. Vaccine efficacy was shown against illness meeting case definition 1 at 80% (94% CI, 52–93%), against case definition 2 at 75% (94% CI, 50–89%) and against case definition 3 at 70% (94% CI, 44–85%). Serious adverse events, events leading to early discontinuation, and fatal adverse events were similar in both groups. None of the events were considered by the investigator of the study to be related to the intervention. Solicited events, primarily injection-site pain or tenderness, were 38% in the vaccine group and 8% in the placebo group. The most common systemic adverse events included fatigue, headache, and myalgia for both the vaccine group (41%) and the placebo group (16%). EBP

Celina Chapman, MD
Richard DeCurtis, MD
Rachael Solomon, MD
Jacqueline Vardaros, PharmD
Southern Illinois University Family Medicine Quincy, Quincy, IL

The corresponding author is Jacqueline Vardaros; jvardaros37@siumed.edu
The authors declare no conflicts of interest.

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In patients with high blood pressure, are ACE-I/ARB more effective than CCB in reducing systolic blood pressure?

EVIDENCE-BASED ANSWER

No. No clinical difference was noted in reduction of systolic blood pressure between calcium channel blockers (CCBs) and ACE-Is/angiotensin receptor blockers (ARBs; SOR: **C**, meta-analysis of studies with disease-oriented outcomes). No difference is noted in all-cause mortality or pooled major cardiovascular outcomes between these classes of antihypertensives. CCBs slightly increase the incidence of heart failure when compared with ACE-I/ARB. CCBs slightly reduce stroke rate compared with ACE-I with no difference compared with ARB (SOR: **A**, meta-analysis).

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

A 2022 systematic review of 23 randomized controlled trials (RCTs; N=153,849) evaluated the effect of calcium channel blockers (CCBs) on prevention of cardiovascular events compared with other antihypertensive drugs including ACE-Is and ARBs.[1] The review included adult patients with hypertension (defined as BP >140/90 mmHg) treated with an antihypertensive agent for at least one year. Primary outcomes included stroke, myocardial infarction, congestive heart failure (CHF), total major cardiovascular events, and all-cause mortality. Reduction in systolic blood pressure (SBP) was a secondary outcome. CCBs exhibited greater reduction in SBP than ACE-Is (4 trials, N=9,570; mean difference [MD] –1.1 mmHg; 95% CI, –1.4 to –0.82) and ARB (1 trial, n=7,596; MD –2.1 mmHg; 95% CI, –2.5 to –1.7). Despite statistical significance, a reduction of 1 or 2 mmHg is unlikely clinically relevant. Furthermore, considerable heterogeneity of treatment effect was noted among trials comparing CCBs and ACE-Is. Regarding primary outcomes, patients treated with a CCB had a lower risk of developing stroke than those treated with an ACE-I (7 trials, N=2,799; relative risk [RR] 0.90; 95% CI, 0.81–0.99), but no significant difference compared with those treated with an ARB (6 trials, N=25,611; RR 0.87; 95% CI, 0.76–1.0). Patients treated with a CCB had a higher risk of developing CHF than patients treated with an ACE-I (5 trials, N=25,276; RR 1.2; 95% CI, 1.1–1.3) or an ARB (5 trials, N=23,265; RR 1.2; 95% CI, 1.1–1.4). No significant difference was noted in total major cardiovascular events or all-cause mortality when CCBs were compared with ACE-Is or ARBs.

A 2005 RCT (n=267) compared the effectiveness of low-dose CCB nifedipine gastrointestinal therapeutic system (GITS) versus the ACE-I enalapril on the reduction in BP.[2] Adults 22 years old and older with mild-to-moderate hypertension, defined as systolic BP 140 to 179 mmHg and diastolic BP 90 to 109 mmHg were included. Patients were treated with nifedipine GITS 20 mg by mouth once daily or enalapril 20 mg by mouth once daily for 12 weeks. The researchers measured change in BP from baseline using sitting BP in clinic. Similar effectiveness of nifedipine and enalapril in reduction of sitting SBP compared with baseline was noted (MD –1.0 mmHg, P=.36). Adverse events were reported at similar rates, most frequently cough for enalapril and abnormal liver function tests for nifedipine.

A 2007 RCT (n=303) compared the antihypertensive efficacy of the ACE-I zofenopril with the CCB amlodipine.[3] Patients 18 to 75 years old identified as having mild-to-moderate hypertension, defined as diastolic BP 95 to 109 mmHg were included. Patients with secondary hypertension, insulin-dependent diabetes, or taking other antihypertensives were excluded. Medication doses were zofenopril 30 to 60 mg once daily or amlodipine 5 to 10 mg once daily. After treatment, BP was monitored at 2, 4, 6, 8, and 12 weeks. After 12 weeks of treatment, similar effectiveness of zofenopril and amlodipine in reduction of SBP was noted (MD –1.5 mmHg, P=.46). Adverse events were reported with similar frequency, most commonly headache and edema for amlodipine and headache and cough for zofenopril.

Findings from the RCTs and systematic review above were consistent with the 2017 American College of Cardiology/American Heart Association evidence-based guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. This guideline recommended that thiazide diuretics, ACE-Is, ARBs, or CCBs are all first-line antihypertensive medications (grade A, substantial high certainty evidence).[4] EBP

Alice M Boshoven, MD
Megan Everson, MD
Shelby VanRossum, MD
Kevin Izquierdo, DO
Fox Valley Family Medicine Residency, Appleton, WI

The corresponding author is Alice Boshoven; alice.boshoven@mosaicfamilyhealth.org.
The authors declare no conflicts of interest.

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Does long-term use of creatine for athletic performance have adverse effects in adult athletes?

EVIDENCE-BASED ANSWER

Based on limited evidence, long-term use of creatine monohydrate up to five years seems safe in collegiate athletes and in adults over 65 years old engaged in resistance training (SOR: **C**, small randomized and nonrandomized controlled trials and consensus practice guideline).

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

A 2007 double-blinded randomized controlled trial evaluated 39 adults 65 to 85 years old to examine the effects of a six-month resistance exercise training program supplemented with creatine monohydrate (CrM) and conjugated linoleic acid (CLA) or a placebo.[1] Participants were randomly assigned to receive CrM (5 g/day) + CLA (6 g/d; n=21) or a placebo (n=18) and engaged in supervised resistance training twice weekly. Assessments were conducted over three separate visits for pretesting and posttesting. These included measurements of strength, muscular endurance, functional tasks, body composition, and laboratory investigations. The study used various statistical analyses including an unpaired *t*-test, a three-way ANOVA with post hoc Tukey's Honestly Significant Difference (HSD) analysis, and Pearson's R correlation to examine subject characteristics, body composition, strength variables, and their correlations with blood and urine markers. The intervention group exhibited with no change in creatinine clearance, suggesting no adverse effect on renal function. No significant differences were observed between the intervention and placebo groups regarding clinical or laboratory safety signals. The study's small sample size, short duration, advanced age of participants, absence of athletes, and lack of a group receiving CrM without CLA supplementation may limit the generalizability and the ability to draw firm conclusions regarding long-term safety.

A 2003 open-label, nonrandomized controlled trial of 98 NCAA Division IA college football players evaluated the effects of creatine supplementation over a 21-month training period.[2] The study compared 54 blood and urine markers of health among athletes who self-selected creatine supplementation for zero to six months (n=12), 7 to 12 months (n=25), 12 to 21 months (n=17), and those with no creatine use (n=44). After a loading dose of 15.75 g/d for the first five days of the study, athletes in the creatine supplementation groups were administered an average of 5 g/d of creatine monohydrate. Fasting blood and 24-hour urine samples were collected voluntarily at multiple time points throughout the 21-month study period. Subjects were categorized based on creatine usage duration, and their baseline and final blood and urine samples were analyzed using multivariate analysis of variance (MANOVA) and 2×2 repeated-measures ANOVA univariate tests. No significant difference was observed between the creatine and noncreatine groups in the health markers. Although the study concluded that long-term creatine use did not adversely affect health markers in collegiate football players, the results may have been biased because of self-selection in the various supplementation groups. A further limitation of this study includes the small number of participants (n=17) who took creatine for 12 to 21 months.

A 2017 literature review by the International Society of Sports Nutrition (ISSN) assessed the role and safety of creatine supplementation across all age groups.[3] The conclusions were drawn from nonsystematic literature reviews conducted by content experts, including ISSN members. Their findings suggested that long-term use of creatine monohydrate, at doses of up to 30 g/d for 5 years, did not exhibit any consistent pattern of adverse health risks among healthy individuals. However, a noted limitation was the potential conflict of interest because some authors received research grants from companies selling creatine and served as paid consultants in the industry. The authors of this guideline did not include indicators for the grade of evidence. However, given that this guideline recommendation is based primarily on expert opinion, the guideline is consistent with strength of recommendation (SOR) **C**. EBP

Kumi Yuki, MD
Allison M Bernard, PharmD, BCACP
Nathan A. Shaw, MD
University of Iowa Family Medicine Department, Iowa City, IA

The corresponding author is Kumi Yuki, MD; kumi-yuki@uiowa.edu
The authors declare no conflicts of interest.

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Does hypoglossal nerve stimulation decrease disease severity in those with obstructive sleep apnea?

EVIDENCE-BASED ANSWER

Yes. Hypoglossal nerve stimulation (HNS) reduces obstructive sleep apnea (OSA) severity by up to 54% and daytime sleepiness symptoms by up to 44% (SOR: B, meta-analysis of prospective cohort studies). Treatment is effective across a wide range of OSA severities (SOR: C, large retrospective cohort study). The effect on apnea frequencies is similar to positive airway pressure, although HNS may reduce daytime sleepiness symptoms more (SOR: C, prospective cohort study).

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

A 2020 meta-analysis of 12 prospective cohort studies (N=350) examined the effects of hypoglossal nerve stimulation (HNS) on obstructive sleep apnea (OSA) severity and symptoms.[1] All patients were adults, although other inclusion criteria varied with most studies including patients previously failing PAP therapy, with pretreatment apnea-hypopnea index (AHI; average number of apnea or hypopnea events per hour) greater than 20/hr and body mass index (BMI) less than 40 kg/m^2. The studied intervention was implantation of any HNS device (brands included Inspire, ImThera, and Apnex). The various devices work similarly, all being implanted under the skin and using electrical stimulation at the base of the tongue with each breath to move the tongue forward, decreasing airway obstructions. No control or comparison group was present. Outcomes included change in severity of sleep apnea measured by AHI and change in daytime somnolence measured by the Epworth sleepiness scale (ESS; range 0–24, ≥10 abnormal). Follow-up ranged from six to 12 months. Long-term data up to 60 months were reported by the authors but did not include significance statistics. Twelve months after implantation, all three devices reduced AHI by an average of 44% to 56% (Inspire: 7 studies, N=346; mean difference [MD] -18/hr; 95% CI, -20 to -15/hr; ImThera: 2 studies, N=56; MD -24/hr; 95% CI, -37 to -11/hr; Apnex: 3 studies, N=81; MD -20/hr; 95% CI, -30 to -11/hr). Two devices reduced ESS at 12 months: Inspire by 44% (3 studies, N=211; MD -5.3; 95% CI, -6.2 to -4.4) and Apnex by 35% (1 study, n=31; MD -4.2; 95% CI, -6.3 to -2.1), while ImThera did not significantly reduce ESS. The only serious complication noted was the need to have surgical repositioning of the leads in 6% of patients. Other less serious adverse effects included discomfort due to electrical stimulation (60%) and tongue abrasions (27%). Limitations included the observational design of the included trials without a comparison group, limited long-term data, and treatment limited to highly specialized academic centers, affecting generalizability.

A 2022 multicenter retrospective cohort study (n=1,963) examined the effect of HNS on OSA symptoms across various severities.[2] Researchers included adult patients who had undergone implantation of the Inspire brand HNS device. The median age of included patients was 60 years old, 73% were male, 94% were White, the average pretreatment AHI was 33/hr, and the average pretreatment ESS was 11. Researchers divided patients into five subgroups based on pretreatment AHI (0–15/hr, 16–30/hr, 31–50/hr, 51–65/hr, and >65/hr). The studied outcomes included percent of patients achieving treatment success defined by Sher's criteria (≥50% reduction in AHI and post-treatment AHI <20/hr) and reduction in ESS score one year postimplantation. Subgroup analysis was performed on the five pretreatment severity groups. Considering all patients together one year after implantation, 67% of patients achieved treatment success and there was a median reduction in ESS of 45% (pretreatment 11 vs post-treatment 6; $P<.0001$). No significant difference was observed in outcomes between the five severity groups. Limitations of this study included a lack of true comparison group, significant demographic variation among subgroups which could reflect sampling error, and the use of a single manufacturer's device.

A 2022 multicenter prospective cohort study (n=227) compared HNS with PAP therapy in patients with OSA.[3] Researchers included adults diagnosed with OSA and an ESS score of at least 11, treated either with HNS or with PAP exclusively for at least 12 months. Researchers excluded patients with BMI over 35 kg/m^2, AHI less than 15/hr or greater than 65/hr, anatomical abnormalities, or central sleep apnea. Patients in the HNS group had previously failed PAP therapy due to nonadherence or persistent symptoms despite adherence. Researchers used propensity score matching to assemble a comparison group similar in factors known to affect OSA (ie, age, pretreatment AHI, BMI), who were being treated with PAP therapy as first line for OSA. Studied outcomes included reduction in AHI and ESS after 12 months of therapy. Both treatments resulted in a significant reduction in AHI, but the magnitude of the effect was similar between the two groups (HNS: 8.1/hr; PAP: 6.6/hr). Patients in the HNS group had a 25% greater reduction in ESS compared with those receiving PAP therapy (–8.0 vs –3.9; $P=.042$). The study was limited by its observational design and increased risk for selection bias. EBP

Haley Crosby, MD[1]
Josh Smothers, MD[2]
[1]University of Missouri School of Medicine, Columbia, MO
[2]Department of Family Medicine, University of Missouri School of Medicine, Columbia, MO

The corresponding author is Josh Smothers MD, jsmothers@health.missouri.edu
The authors declare no conflicts of interest.

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Is coenzyme Q10 supplementation effective for migraine prophylaxis compared with placebo?

EVIDENCE-BASED ANSWER

Coenzyme Q10 supplementation may decrease the frequency of migraines by roughly 1.5 days per month and duration of headaches anywhere between 12 and 42 minutes. Coenzyme Q10 supplementation does not improve severity of migraine headaches (SOR: **A**, two meta-analyses).

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

In 2021, a meta-analysis of six randomized controlled trials (RCTs; N=371) compared the efficacy of coenzyme Q10 (CoQ10) supplementation for reduction in severity, frequency, and duration of migraines in adults compared with placebo.[1] The review included studies with adult patients (18–50 years old) diagnosed with migraines by the International Headache Society criteria. Patients were supplemented with varying dosages (30–800 mg daily) of either liquid or capsule CoQ10 exclusively or in combination with other supplements compared with placebo. Treatment times ranged from eight weeks to three months. All trials excluded individuals on migraine preventive drugs in prior six months or use of CoQ10 in the prior three months to enrollment. Crossover designs and controlled clinical trials were excluded. In addition to severity, frequency, and duration of migraines and headaches, one study evaluated the number of days with nausea because of migraine headache and the number of acute migraine medications used during the study period. Another study also measured the quality of life among patients with migraine headaches. Researchers assessed quality of life using scores from the Migraine Specific Quality of Life questionnaire (MSQ), Headache Impact Test (HIT-6), and Migraine Disability Assessment

Questionnaire (MIDAS). The MSQ is scored 0 to 100, with higher scores correlating to better quality of life. The HIT-6 is scored from 36 to 49, with higher scores indicating more severe effects of migraines. The MIDAS is scored from 0 to 35, with higher scores representing severe disability. CoQ10 decreased duration of headaches (6 studies, N=371; mean difference [MD] –0.19 hour; 95% CI, –0.27 to –0.11) and frequency of migraine headaches per month (5 studies, N=259; MD –1.52; 95% CI, –2.4 to –0.65). CoQ10 also decreased the number of days with nausea because of migraines (1 study, n=42; MD –1.7; 95% CI, –2.92 to –0.48). The number of acute migraine medications used during the study period was not affected by CoQ10. CoQ10 supplementation did not improve severity of headaches. There was no improvement in MSQ questionnaire scores with CoQ10 supplementation; however, improvement was demonstrated in both HIT-6 (1 study, n=77; MD –4.29; 95% CI, –7.19 to –1.39) and MIDAS score (1 study, n=77; MD –6.00; 95% CI, –9.93 to –2.07). Side effects were reported in only one study and included diarrhea and chromaturia, with no demonstrated difference between control and intervention groups. Three trials had unclear risk for detection bias, and one trial had high risk of attrition and reporting bias. Other potential limitations included lack of consensus regarding dosage of CoQ10 supplementation, various forms of CoQ10 supplementation used (liquid formulation, mixed with other substances like L-carnitine), and two of the six studies declaring funding from drug manufacturers.

A 2018 meta-analysis including three RCTs and two observational studies (N=346) compared the effects of CoQ10 supplementation on migraines compared with placebo.[2] This study included two RCTs in overlap with the previously reviewed study. The meta-analysis included trials in which the patients (10–44 years old) were diagnosed with migraine by the International Classification of Headache Disorders criteria. Patients were supplemented with CoQ10 at varying dosages (100–400 mg daily) for three months. Migraine parameters that the researchers assessed were as follows: migraine attacks per month, migraine severity, migraine days per month, and migraine duration. CoQ10 supplementation did not demonstrate a decrease in migraine attacks per month or migraine severity. CoQ10 supplementation did decrease migraine days per month (1 study, n=73; MD –1.79; 95% CI, –2.34 to –1.24) and migraine duration (3 studies, N=195; MD –0.70 hr; 95% CI, –1.22 to –0.18). There were no side effects with CoQ10 reported. Two RCTs had low risk of bias; one study had high risk of bias given incomplete outcome data. Limitations to this study also included lack of uniformity or consensus regarding dosages of CoQ10 supplemented in the intervention groups. EBP

Jennifer Svarverud, DO, FAAFP
Kayla Mowatt, DO
Nellis AFB Family Medicine Residency Program, Nellis AFB, NV

The corresponding author is Jennifer Svarverud; jsvarverud@gmail.com
The authors declare no conflicts of interest.
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Do self-collected HPV tests improve rates of cervical cancer screening?

EVIDENCE-BASED ANSWER

Human papillomavirus (HPV) self-sampling may increase cervical cancer screening uptake when compared with standard of care, with no impact on further clinical assessment or treatment (SOR: **B**, meta-analysis of randomized controlled trials [RCTs] and observational studies with high heterogeneity). Mailed HPV self-collection kits with scheduling assistance resulted in greater completion of cervical cancer screening than scheduling assistance alone in under screened women from low-income backgrounds (SOR: **B**, single RCT).

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

A 2019 meta-analysis of 33 studies (29 randomized controlled trials [RCTs], 3 cohort, and 1 cross-sectional) assessed the impact of human papillomavirus (HPV) self-sampling on cervical cancer screening among adult women (N=369,017).[1] Studies included women 30 to 60 years old mainly from wealthy countries but mostly not participating in routine cervical cancer screening. The analysis compared HPV self-sampling to standard care methods. Self-sampling dissemination strategies included a mailed kit directly to the home, kit offered door-to-door by a healthcare worker, or a kit offered on demand to be picked up at a designated location. Kits included self-collected HPV methods by brush, swab, and lavage. Standard care cervical cancer screening used provider collected screening by cytology (Papanicolaou smear), provider collected HPV testing, or provider visual inspection with acetic acid. Outcomes included rates of cervical cancer screening, follow-up after positive cervical cancer screening, social harms, and adverse events. HPV self-sampling lead to greater screening uptake compared with standard care methods (29 trials, N=307,866; relative risk [RR] 2.1; 95% CI, 1.9–2.4; I^2=99%). The effect size varied depending on the method of HPV test kit dissemination, whether mailed directly to the home (23 trials, N=250,031; RR 2.3; 95% CI, 1.9–2.7; I^2=99%), offered door-to-door (5 trials, N=32,238; RR 2.4; 95% CI, 1.1–5.0; $I^{2=}$99.7%), or requested on demand (5 RCTs, N=88,222; RR 1.3; 95% CI, 0.9–1.8; I^2=98%). No difference was noted in rates of clinical follow-up after positive cervical cancer screening (5 trials, N=76,328; RR 1.1; 95% CI, 0.8–1.6; I^2=84%). None of the studies reported the occurrence of social harms or adverse events associated with HPV self-sampling. Substantial heterogeneity was noted among the studies included.

A 2023 multicenter, open-label RCT (N=665) evaluated the efficacy of HPV self-collection kits on cervical cancer screening completion versus control.[2] Patients were nonpregnant women with an average age of 42 years old, from a low-income background, with an intact cervix, who were overdue for cervical cancer screening. They were recruited from selected clinics in certain counties within North Carolina. The intervention group received mailed HPV self-collection kits in conjunction with scheduling assistance, whereas the control group received scheduling assistance. The primary outcome was cervical cancer screening completion defined as testing negative for high-risk HPV on self-collected samples or attending a screening appointment, measured at six months after enrollment. Completion of cervical cancer screening was higher in the intervention group than in the control group (72% vs 37%; risk ratio 1.9; 95% CI, 1.6–2.3) in the intention-to-treat analysis. Side effects were minimal and reported in only 1% (3/438). This RCT was limited by self-selecting for more motivated individuals than the general population, an open-label design, and unequal allocation ratio between the intervention and control groups. EBP

Ishaah Talker, MD
Jasmine Davila, MD
Sarah Daly, DO, FAAFP
Utah Valley Family Medicine Residency, Provo, UT

The corresponding author is: Sarah Daly; sarah.daly@imail.org.
The authors declare no conflicts of interest.

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Should antenatal corticosteroids be used in the late preterm period in pregnant patients with pregestational or gestational diabetes?

EVIDENCE-BASED ANSWER

Benefits of betamethasone administration to pregnant patients with pregestational diabetes mellitus (DM) or gestational diabetes mellitus at risk of delivery in the late preterm period remains unclear. Administration of antenatal late preterm steroids in this setting may reduce neonatal respiratory morbidity but may increase the risk of neonatal hypoglycemia and does not appear to reduce the length of hospital stay for neonates born in the late preterm period (SOR: **C**, 2 cohort studies and a secondary analysis of 1 randomized controlled trial).

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Evidence Summary

A 2021 retrospective cohort study (N=123) examined whether antenatal late preterm steroids (ALPS) administration to pregnant patients with diabetes increased the risk of neonatal hypoglycemia.[2] Patients were between 34 and 36 weeks of a singleton gestation and at risk for preterm delivery before 37 weeks. Those with prior courses of antenatal corticosteroids or significant fetal anomalies were excluded. Delivery after 37 weeks was not a reason for exclusion. Neonatal outcomes were compared before (n=58) and after (n=65) the introduction of the ALPS protocol. Patients in the postprotocol cohort received two intramuscular injections of 12 mg of betamethasone 24 hours apart if there was significant risk of delivery before 37 weeks of gestation. The primary outcome was incidence of neonatal hypoglycemia (glucose of 60 mg/dL or lower) within the first 24 hours of life with secondary outcomes including glucose of 40 mg/dL or lower, transient tachypnea of the newborn, respiratory distress syndrome, surfactant administration, and hospital length of stay. Neonates in the postprotocol period experienced a significantly higher incidence of hypoglycemia compared with the preprotocol period (82% vs 60%, P=.008). In a sensitivity analysis (50 of 65 eligible patients in postprotocol period received ALPS), frequencies of hypoglycemia were significantly higher in the postprotocol period than in the preprotocol period at both the 60 mg/dL level (80% vs 60%, P=.03) and at the 40 mg/dL level (51% vs 29%, P=.02). No significant difference was found among secondary outcomes in either type of analysis. Limitations of this study included unknown maternal glucose levels during labor and unknown reasons for deviation from ALPS administration in the postprotocol period among 15 of the 65 patients (23%).

A 2019 secondary analysis (n=306) of a multicentered randomized controlled trial compared neonatal respiratory morbidity in the first 72 hours of life between patients with diagnosed gestational diabetes mellitus (GDM) and those without.[1] Patients who received previous antenatal glucocorticoids, had preexisting diabetes mellitus (DM), or had a delivery expected within 12 hours of presentation were excluded. Patients at risk of delivering in the late-preterm period were randomized to receive two intramuscular injections 24 hours apart of either 12 mg of betamethasone or placebo. After adjusting for age, parity, and hypertension, neonates born to women with GDM, compared with neonates born to women without GDM, did not differ in terms of respiratory morbidity when receiving antenatal late preterm delivery steroids (adjusted risk ratio [RR] 0.84; 95% CI, 0.61-1.2). The authors concluded that pregnant patients with GDM should receive ALPS for threatened late preterm birth similarly to pregnant patients without GDM.

A 2020 three-site retrospective cohort study (n=54) analyzed outcomes of patients with singleton pregnancies and preexisting DM who delivered in the late preterm period.[3] Patients with fetal congenital anomalies and antenatal or intrapartum stillbirths were excluded. Of the 54 dyads who met inclusion criteria, 18 of these patients (33%) received betamethasone in the late preterm period, while the remaining 36 patients did not. The authors found no difference in length of hospital stay for neonates in the group that received betamethasone compared with the control group (mean 6.1 vs 4.5 days, P=.23). Respiratory morbidity was not significantly different between the group that received betamethasone and the one that did not (50% vs 25%, P=.066). No difference was observed in neonatal hypoglycemia between the betamethasone and control groups (50% vs 47%, P=.8). EBP

Neil S. Cornwell
Victoria L. Boggiano, MD, MPH
Sarah T. Wright, MLS
Narges Farahi, MD
University of North Carolina, Chapel Hill, NC

The corresponding author is Victoria Boggiano; Victoria.boggiano@unchealth.unc.edu.
The authors declare no conflicts of interest.

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Is patiromer a safe and effective treatment for hyperkalemia in patients with heart failure (HF) on goal-directed medical therapy?

EVIDENCE-BASED ANSWER

Patiromer has a small lowering effect on potassium values and hyperkalemia (>5.5 mmol/L) incidence. It also increases the likelihood of optimizing renin–angiotensin–aldosterone system inhibitor therapy (SOR C, systematic review/meta-analysis of disease-oriented outcomes). Patiromer increases the risk of hypokalemia but has no effect on all-cause mortality (SOR C, systematic review/meta-analysis of disease-oriented outcomes).

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

In 2023, a systematic review and meta-analysis of 6 randomized controlled trials (RCTs) (N=1,432) compared the safety and efficacy of new potassium binders with placebo for the treatment of adults with hyperkalemia and heart failure.[1] The meta-analysis included RCT evaluating patiromer or sodium zirconium cyclosilicate in patients with heart failure at high risk of hyperkalemia. Outcomes studied included renin–angiotensin–aldosterone system inhibitor (RAASi) treatment optimization, incidence of hyperkalemia (>5.5 mmol/L), incidence of hypokalemia (<3.5 mmol/L), and all-cause mortality. New potassium binders increased rates of RAASi treatment optimization (risk ratio [RR] 1.14; 95% CI 1.02–1.28), reduced the risk of hyperkalemia (RR 0.66; 95% CI 0.52–0.84), and increased the risk of hypokalemia (RR 5.61, 95% CI 1.49–21.08). There was no effect on all-cause mortality. Adverse events, other than hyperkalemia, were similar between groups. Limitations of the study are that a single RCT comprised >50% of the total number of patients, variable follow-up periods from 4 to 27 weeks, and different definitions of RAASi optimization.

In 2023, another systematic review and meta-analysis of 4 RCTs (N=1,163) compared the safety and efficacy of patiromer with placebo for the treatment of heart failure patients with hyperkalemia.[2] The review included trials if they were RCTs, involved patients with heart failure, examined patiromer for hyperkalemia or RAASi therapy, and compared patiromer with placebo. The primary outcome was reduced incidence of hyperkalemia defined as >5.5 mmol/L. Secondary outcomes included target dose of RAASi therapy and decrement of RAASi therapy. Patiromer showed a 44% reduction in the risk of hyperkalemia (RR 0.56, 95% CI, 0.36–0.87), patiromer increased tolerance of target doses of MRA (RR 1.15, 95% CI 1.02–1.30), and patiromer decreased the incidence of MRA decrement (HR 0.62, 95% CI 0.45–0.87). Safety outcomes reported examined any and serious adverse events, mortality, and hypokalemia. Patiromer increased risk of hypokalemia (RR 1.51, 95% CI 1.07–2.12) but no other safety outcomes. Limitations of the study note one of the trials was single blinded, 2 of the trials were of short duration (<8 weeks), and all were industry sponsored.

In 2022, a multicenter RCT (n=878) examined the effectiveness of patiromer for hyperkalemia compared with placebo.[3] Patients were adults recruited from the

USA, South America, Europe, and Russia with New York Heart Association (NYHA) Class II–IV heart failure and a left ventricular ejection fraction ≤40% having hyperkalemia (potassium >5.0 mmol/L on 2 occasions). The mean age was 67 years. Patients were taking an angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), angiotensin receptor–neprilysin inhibitor (ARNi), and/or mineralocorticoid receptor antagonists (MRA). The intervention group received patiromer, titrated up to 25.2 g, while the control group received placebo powder. Both underwent optimization of RAASi therapy by titrating MRA to ≥50 mg/day and titrating ACEi/ARB to ≥50% of recommended doses. The primary outcome was mean change in serum potassium, and the secondary outcomes were hyperkalemia >5.5 mmol/L, maintained MRA target dose, and total number of hyperkalemia events. The patiromer group serum potassium mean was –0.10 mmol/L compared with placebo (95% CI, –0.13 to –0.07). Patiromer decreased the risk of hyperkalemia >5.5 mmol/L (hazard ratio [HR] 0.63 [0.45–0.87]), reduced the likelihood of reduced MRA dose (HR 0.62 [0.45–0.87]), and lowered the number of total hyperkalemia events (HR 0.66 [0.53–0.81]). Adverse events reported showed higher hypokalemia in the patiromer group. The RCT reported the primary and secondary endpoints were affected due to the COVID-19 pandemic and due to reduced recruitment and supply chain issues. This study was funded by a pharmaceutical company that manufactures patiromer. EBP

Mark Wirtz, MD
University of Wisconsin Madison, Madison, WI

The corresponding author is Mark Wirtz, MD; mark.wirtz@fammed.wisc.edu.
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Are topical NSAIDs as effective as oral NSAIDs for treatment of osteoarthritis pain in adults?

EVIDENCE-BASED ANSWER

Topical formulations of non-steroidal anti-inflammatory drugs (NSAIDs) seem to be equally as effective as oral NSAIDs for the treatment of osteoarthritis pain. Topical NSAIDs have significantly lower risk for gastrointestinal adverse events with no increase in local adverse events (SOR: **A**, multiple meta-analyses of randomized controlled trials [RCTs]).

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

A 2022 meta-analysis of eight randomized controlled trials (RCTs) (N=2,096) evaluated the efficacy and safety of topical and oral non-steroidal anti-inflammatory drugs (NSAIDs).[1] Patients were 40 years old and older, with roughly two-thirds being female. Patients were included if they had radiological evidence for osteoarthritis (OA), had a history of moderate pain for at least one month, and morning stiffness for at least 30 minutes. Trials excluded patients with NSAID allergy or with other types of arthritis. Patients in the intervention groups received topical NSAIDs such as diclofenac 1.5% solution and ibuprofen 4% gel. The other groups of patients received oral NSAIDs such as celecoxib 100 mg or ibuprofen 800 mg. The treatment duration was required to be at least two weeks, and other analgesics were forbidden. The primary outcome was patients' subjective perception of pain measured using a 100-mm visual analog scale (VAS, higher scores indicating more pain) and the OA index of the universities of Western Ontario and McMaster (WOMAC; range 0–4, a higher score indicating more pain). No significant differences were observed in VAS scores (3 trials, N=424; standardized mean difference [SMD] –0.01; 95% CI, –0.02 to 0.18; I^2=0%) and WOMAC scores (5 trials, N=1,622; SMD 0.07; 95% CI, –0.02–0.17; I^2=0%) between oral and topical NSAIDs. Topical NSAIDs had a lower higher risk of gastrointestinal adverse events than oral NSAIDs (7 trials, N=1,946; OR=0.30, 95% CI, 0.16–0.56). The study was limited by the fact that the trials used different NSAIDs, and the timing and frequency of administration varied greatly.

A 2004 meta-analysis of 25 RCTs (N=2,264, 1 RCT included above) evaluated the efficacy and safety of topical NSAID when compared with placebo and oral NSAIDs.[2] Of 25 RCTs, only three trials (N=764) compared topical with oral NSAIDs. Patients were predominantly older than 40 years old, and no other specific demographic information was provided. Patients were included if they had moderate-to-severe chronic pain resulting from musculoskeletal disorders. Topical treatment was at least once daily, and duration was two weeks or longer. Researchers excluded trials less than seven days and patients with severe OA. Patients in the intervention groups received piroxicam 0.5% gel, 1% gel, or eltenac 1% gel. Patients in the control group received oral ibuprofen 1,200 mg daily or oral diclofenac 100 mg daily. The primary outcome was a 50% reduction in pain at two weeks measured on a categorical scale by using "none" or "slight" pain at rest or with movement (or comparable wording). The secondary outcomes included local or systemic adverse events reported by patients post-treatment. No significant difference was observed in the primary outcome between topical and oral NSAID therapy (3 RCTs, N=764; relative risk [RR] 1.1; 95% CI 0.9–1.3; I^2 not provided). No significant differences in local adverse events (2 RCTs, N=443; RR 3.0; 95% CI 1.1–8.5; I^2 not provided) and systemic adverse events (3 RCTs, N=764; RR 0.83; 95% CI 0.6–1.1; I^2 not provided) between the two groups were observed. This study was limited by inconsistency in outcome measures across trials. EBP

Khaled Kudsi, DO
Erik Weitz, DO
Beaumont Health Family Medicine Residency, Troy, MI

The corresponding author is Erik Weitz, erik.weitz@corewell-health.org
The authors declare no conflicts of interest.

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