December 2023

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

December 2023
Volume 26 | Number 12

EVIDENCE-BASED PRACTICE
December 2023
Volume 26 | Number 12

FPIN
Family Physicians Inquiries Network

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

TABLE OF CONTENTS

VOL 26 | NO. 12 | December 2023

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

EBP FEATURES

DIVING FOR PURLs

IN DEPTH

GEMS

HELPDESK ANSWERS

SPOTLIGHT ON PHARMACY

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

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

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

STATEMENT OF PURPOSE

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

DISCLOSURE

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

What is the most effective type of therapy for PTSD in refugee populations?

EVIDENCE-BASED ANSWER

Both cognitive behavioral therapy (CBT) with a trauma-based focus and eye movement desensitization and reprocessing (EMDR) are effective for treatment of PTSD in refugee populations, with CBT appearing to be more effective than EMDR (strength of recommendation [SOR]: **A**, network meta-analysis of randomized controlled trials [RCTs]). Narrative exposure therapy, a subtype of CBT, is the most effective treatment of PSTD in high-income countries (SOR: **A**, meta-analysis of RCTs).

DOI 10.1097/EBP.0000000000001849

Evidence summary

Over 27 million people were displaced in 2021 based on data from the United Nations High Council on Refugees (UNHCR).[1] Up to 36% of these refugees are expected to experience symptoms of PTSD.[2] A 2021 systematic review and network meta-analysis of 23 randomized controlled studies evaluated effectiveness of different treatment modalities in refugee and asylum-seeker populations.[3] The treatment modalities included cognitive behavioral therapy (CBT), eye movement desensitization and reprocessing (EMDR), narrative exposure therapy (NET), cognitive restructuring, exposure therapy, stress inoculation training, stabilization therapy, stress management, coffee and family education and support, and Self-Help + (the World Health Organization's 5-session stress management course for large groups), in addition to supportive and trauma counseling. This meta-analysis included over 2,300 participants from both high-income (two-third of studies) and low-income countries (one-third of studies), with the primary outcome being presence of PTSD symptoms after implementation of these interventions. Outcome measures included the Clinician-Administered PTSD Scale (CAPS-5); if not available, the Harvard Trauma Questionnaire or other PTSD rating scales based on DSM or ICD criteria were used. The interventions were compared against waitlist (WL, 11 of 23 studies), treatment as usual (TAU, any intervention that reflects the usual care in each treatment setting, 9 of 23 studies), or no treatment. Measurement of postintervention outcomes took place after at least four months in 17 of 23 studies. Participant regions of origin included Africa, the Middle East, and the Balkans, with a smaller segment coming from Asia. Eleven studies also included contemporaneous pharmacological interventions. Because the studies in this network meta-analysis used different rating scales, standardized mean differences (SMDs) were used for outcomes. The more negative the SMD, the more effective a particular treatment was at lowering the score on an outcome measuring tool. In network meta-analysis, the SMDs for CBT, EMDR, and TAU were –1.41 (95% confidence interval [CI], –2.43 to –0.38), –1.30 (95% CI,–2.40 to –0.20), and 0.11, respectively, when compared with waitlist. Most of these studies were deemed to be low risk of bias based on the Cochrane risk of bias tool although heterogeneity was high.

According to a 2017 systematic review and meta-analysis of 12 randomized controlled trials (RCTs)[4] (n=543), NET, a derivative of CBT, was considered the best supported approach in high-income countries. Notably, significant overlap (10 of 23 studies) was noted between this meta-analysis and the 2021 meta-analysis described above. However, the 2017 systematic review focused strictly on refugees resettled to high-income countries. This systematic review showed that all psychosocial interventions (NET, EMDR, CBT, etc) were effective in decreasing PSTD symptoms compared with inactive controls (SMD –1.03; 95% CI, –1.55 to –0.51), with magnitude of effect equaling NNT of 4.4. The primary outcome measured was the mean PTSD symptom ratings scale (using CAPS-5 and HTQ) after implementation of these treatment modalities compared with TAU or wait list as control groups. Five of 12 studies included outcomes before four months (at 2 or 3 months), and 7 of 12 studies measured outcomes at or greater than a four-month interval (with most measurements taking place after 6 months). Average number of in-person sessions for a participant in these studies was 17, with a range of 3 to 25 sessions. NET with a trauma focus was the best supported modality based on five RCTs (n=187), with SMD of –0.78 (95% CI, –1.18 to –0.38; I^2=37%; NNT=6.7. EBP

Lashika Yogendran, MD, MS
Yusuf Abdullah, DO
Sarina Schrager, MD, MS
Department of Family Medicine and Community Health, University of Wisconsin, Madison, WI

The corresponding author is Lashika Yogendran; lashika.yogendran@fammed.wisc.edu.
The authors declare no conflicts of interest.

References

1. *Refugee Statistics*. USA for UNHCR. Accessed October 13, 2022. https://www.unrefugees.org/refugee-facts/statistics/#:~:text=By%20the%20end%20of%202021,53.2%20million%20internally%20displaced%20people. [STEP 5]
2. Turrini G, Purgato M, Ballette F, Nosè M, Ostuzzi G, Barbui C. Common mental disorders in asylum seekers and refugees: umbrella review of prevalence and intervention studies. *Int J Ment Health Syst.* 2017;11:51. [STEP 1]
3. Turrini G, Tedeschi F, Cuijpers P, et al. A network meta-analysis of psychosocial interventions for refugees and asylum seekers with PTSD. *BMJ Glob Health.* 2021;6(6):e005029. [STEP 2]
4. Nosè M, Ballette F, Bighelli I, et al. Psychosocial interventions for post-traumatic stress disorder in refugees and asylum seekers resettled in high-income countries: systematic review and meta analysis. *PLoS One*. 2017;12(2):e0171030. [STEP 1]

Combating Recurrent UTIs With an Army of Bacteria

Lorenzo-Gómez MF, Foley S, Nickel JC, et al. Sublingual MV140 for Prevention of Recurrent Urinary Tract Infections. *NEJM Evidence*. 2022; 1(4). doi: 10.1056/EVIDoa2100018

DOI 10.1097/EBP.0000000000001904

This 2022 multicenter, double-blinded, randomized, placebo-controlled trial compared MV140 with placebo in 229 women 18 to 75 years old with recurrent urinary tract infection (UTI). MV140 was self-administered daily sublingually by patients in the two intervention groups, the six-month MV140 treatment group or the three-month MV140 treatment plus three-month placebo group. The control group received a placebo sublingual preparation for six months. The primary outcome was the number of UTI episodes in a nine-month study period after the first three months of intervention. Secondary outcomes included the proportion of patients remaining UTI free, time to first UTI, and analysis of health-related quality of life. In the placebo group, a median number of 3.0 (interquartile range [IQR] 0.5–6.0) UTI episodes per patient were noted in comparison with 0.0 (IQR 0.0–1.0) in both the MV140 treatment groups. The number needed to treat to prevent one UTI was 3.26 in the three-month MV140 treatment group and was 3.03 in the six-month MV140 treatment group. In the MV140 treatment groups, 39 of 70 patients in the three-month intervention (56%; 95% CI, 44% to 67%) and 40 of 69 participants in the six-month intervention (58%; 95% CI, 44% to 67%) remained UTI free compared with 19 of 76 participants in the placebo group (25%; 95% CI, 15% to 35%).

Methods

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

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

Bottom line: Although MV140 shows promise for reducing UTI incidence, MV140 is currently not widely available for prescription and thus is not immediately implementable.

Courtney Goettel, MD
UPMC St. Margaret Family Medicine Residency Program, Pittsburgh, PA

The corresponding author is Yufei Ge; yufeige@gmail.com
The author declares no conflict of interest.

Role of inhalers in preserved lung function

Han MK, Ye W, Wang D, et al. Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function. *N Engl J Med*. 2022; 387(13):1173-1184. doi:10.1056/NEJMoa2204752

DOI 10.1097/EBP.0000000000001983

This multisite, randomized, controlled trial compared inhaled dual bronchodilator therapy to placebo among 535 symptomatic adults 40 to 80 years old with a >10 pack-year history of tobacco use and preserved lung function on spirometry (defined by FEV1/FVC >0.70 and FVC >70% after bronchodilator use). Symptomatic patients were defined as having a COPD assessment test (CAT) score of at least 10 (scores range from 0 to 40, with higher scores indicating worse symptoms). Patients were excluded for a diagnosis of asthma or other known lung disease as were those already using any combination of long-acting or short-acting agents or inhaled steroids who could not undergo a 30-day washout period before the study onset. Patients were randomized in a 1:1 ratio to receive a combination of inhaled indacaterol (27.5 μg) and glycopyrrolate (15.6 μg) or placebo twice a day for 12 weeks. The primary outcome measured was a 4-point decrease (ie, improvement) in the St. George's Respiratory Questionnaire score (0–100) with 128 of 227 (56.4%) in the treatment group and 144 of 244 (59%) in the placebo group achieving this goal, which was not a significant difference. No significant difference was observed for CAT or transition dyspnea index scores. Four serious adverse events occurred in the treatment group and 11 occurred in the placebo group, but none

were deemed potentially related to the treatment or placebo. Limitations of this study were the small number of participants and the lack of evaluation for other causes of symptoms attributed to smoking.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching UptoDate and PubMed with the terms "long acting beta agonist," "long acting muscarinic," "COPD," "smokers," and "spirometry" 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	No

Bottom line: LAMA/LABA use in adult smokers with normal spirometry is no more effective than placebo in controlling respiratory symptoms.

Steven Fox, MD
Rebecca Long, MD
Matthew Rotondo, MD
University of Tennessee College of Medicine, Chattanooga, TN

The corresponding faculty author is Steven Fox, MD, Steven.fox@erlanger.org
The authors declare no conflict of interest.

Eurethra! Dexamethasone decreases renal colic pain

Razi A, Farrokhi E, Lotfabadi P, et al. Dexamethasone and ketorolac compare with ketorolac alone in acute renal colic: A randomized clinical trial. *Am J Emerg Med*. 2022; 58: 245-250. doi:10.1016/j.ajem.2022.05.054

DOI 10.1097/EBP.0000000000001915

This double-blind, randomized, controlled trial compared 8 mg of dexamethasone IV with placebo in 120 patients between 30 and 44 years old presenting to the emergency room with greater than 8 out of 10 pain on a visual analog scale due to renal colic. Patients' symptoms were assessed at baseline, and they were then given either 30 mg ketorolac IV plus placebo or 30 mg of ketorolac IV plus 8 mg dexamethasone IV. Patient symptoms were once again assessed at 30 min and 60 min after treatment. The primary outcome was pain intensity, and the secondary outcomes were grade of vomiting as well as the need for antiemetics or narcotics at the end of the study. Exclusion criteria included pregnancy, analgesic therapy within six h, hemorrhagic diathesis or use of blood thinners, creatinine clearance less than 30, opioid use disorder, acute abdomen, fever, blood pressure of >180/100 mmHg, and any contraindications to NSAIDs or dexamethasone (such as drug hypersensitivity or adverse effect). Pain scores decreased from 9.5 to 3.5 at 30 min and then to 1 at 60 min in the intervention group, compared with a decrease of 9.5 to 5 at 30 min ($P=.005$) and then to 4 at 60 min ($P=.068$). The need for narcotics 60 min after therapy was 35% in the intervention group compared with 58% in the control ($P=.01$). Need for antiemetics 60 min after therapy was 12% in the intervention and 28% in the control group ($P=.02$). Vomiting grades after therapy were the same in both the groups. Study limitations included follow-up limited to one hour and a lack of standardization for narcotic and antiemetic dosing.

Methods

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

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

Bottom line: Providers may consider adding 8 mg dexamethasone IV to 30 mg ketorolac IV in otherwise healthy adult patients presenting to the ER with severe renal colic who have no contraindications to either therapy. However, it remains unclear after this single study if the addition leads to meaningful outcomes.

Stella Winters, MD
UPMC St. Margaret Family Medicine Residency, Pittsburgh, PA

The Corresponding Faculty Author on the manuscript is: Yufei Ge yufeige@gmail.com
The authors declare no conflict of interest.

Comparing DOACs for atrial fibrillation

Lau WCY, Torre CO, Man KKC, et al. Comparative Effectiveness and Safety Between Apixaban, Dabigatran, Edoxaban, and Rivaroxaban Among Patients With Atrial Fibrillation: A Multinational Population-Based Cohort Study [published correction appears in *Ann Intern Med*. 2022 Dec 6]. *Ann Intern Med*. 2022; 175(11):1515-1524. doi:10.7326/M22-0511.

DOI 10.1097/EBP.0000000000001928

This multinational population-based cohort study directly compared effectiveness and safety outcomes among four direct oral anticoagulants (DOACs) in patients with atrial fibrillation (AF). The study used patient records from five electronic health databases from four countries: France, Germany, the United Kingdom, and the United States covering 221 million patients across primary care, outpatient, and hospital settings. The review included adult patients with newly diagnosed AF who received a new DOAC prescription (N=527,226; apixaban n=281,320; rivaroxaban n=172,176; dabigatran n=61,008; edoxaban n=12,722). Patients were excluded if they had a history of mitral stenosis, hyperthyroidism, mechanical heart valve replacement, transient AF, prescription of warfarin or other DOACs on or within 180 days before the index date, prescription of another oral anticoagulant on the index date, or history of an outcome of interest. Pairs of DOACs were compared in head-to-head target trials. The four outcomes of interest were ischemic stroke and systemic embolism, intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), and all-cause mortality. Median follow-up ranged from 1.5 to nearly 4.5 years. Propensity scoring addressed potential bias because of nonrandomized treatment allocation. No difference was noted among full-dose DOACs in ischemic stroke or systemic embolism, ICH, or all-cause mortality. Apixaban use was associated with lower risk for GIB than dabigatran (hazard ratio [HR] 0.81; 95% CI, 0.70–0.94), rivaroxaban (HR 0.72; 95% CI, 0.66–0.79), or edoxaban (HR 0.77; 95% CI, 0.66–0.91). Among patients who received a reduced dose of a DOAC, rates of ischemic stroke or systemic embolism were lower with dabigatran than rivaroxaban and rates of GIB were lower with apixaban compared with rivaroxaban. In patients with chronic kidney disease, risk for GIB was lower with apixaban than dabigatran or rivaroxaban but not statistically significantly different after propensity score matching. Among patients aged 80 years or older (n=101,397), apixaban use was associated with lower risk for GIB compared with dabigatran (HR 0.65; 95% CI, 0.44–0.95), rivaroxaban (HR 0.64; 95% CI, 0.57–0.72), or edoxaban (HR 0.64; 95% CI, 0.50–0.82). Residual confounding was a potential limitation of the study design.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching DynaMed and UpToDate with the terms "atrial fibrillation" and "DOAC" 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: Use of apixaban in patients with atrial fibrillation is associated with lower rate of GI bleeding and similar rates of ischemic stroke or systemic emboli and intracranial hemorrhage compared with rivaroxaban, dabigatran, and edoxaban. This finding is consistent for chronic kidney disease patients and patients who are 80 years or older. This study confirms but does not provide new evidence of safety nor effectiveness. Multiple guidelines and secondary sources already incorporate similar findings, and clinical practice reflects a growing preference for apixaban.

Muhammad Nauman Riaz, MD
Laura Morris, MD
University of Missouri, Columbia, MO

The Corresponding Faculty Author on the manuscript is: Laura Morris, morrislau@health.missouri.edu
The authors declare no conflict of interest.

Combining SSRIs and oral anticoagulants increases major bleeding events

Rahman AA, He N, Rej S, Platt RW, Renoux C. Concomitant Use of Selective Serotonin Reuptake Inhibitors and Oral Anticoagulants and Risk of Major Bleeding: A Systematic Review and Meta-analysis. *Thromb Haemost*. 2023; 123(1):54-63. doi:10.1055/a-1932-8976

DOI 10.1097/EBP.0000000000001910

This systematic review and meta-analysis included 14 studies, of which ultimately 8 studies were included in the overall meta-analysis reporting. The other 6 studies were excluded from the meta-analysis because measures could not be pooled into an overall hazard ratio (HR). To be included, studies needed to have patients at least 18 years old, concomitant use of SSRIs and oral anticoagulants (OACs), comparison to OACs alone, and have the outcome of major bleeding. Major bleeding was not defined by the authors and was defined in the original studies. OACs could be vitamin K antagonists or direct oral anticoagulants (DOACs). Authors used the Cochrane Risk of Bias Tool to assess bias of included studies. The included studies were either cohort or nested case controlled. Four studies were found to have serious risk of confounding bias; however, overall risk of bias was low for the analysis. Of the 14 studies, cohorts ranged from 73 total patients to 319,855 total patients and were represented from North America, Europe, and Asia. The primary outcome of major bleeding occurred more frequently in the SSRI plus OAC group compared with the OAC group alone (HR 1.35; 95% CI, 1.14–1.58). Similar results were seen for studies graded as low to moderate risk of bias (HR 1.34; 95% CI, 1.11–1.63). In addition, the risk of major bleeding was also seen in patients using DOACs (HR 1.47; 95% CI, 1.03–2.10).

Methods

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

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

Bottom line: Although there is an increased bleed risk when using SSRIs and OACs together, this is not new information as both SSRIs and OACs alone can increase bleed risk. In addition, prescribers are left wondering what the change in practice should be given that both classes of medications are first line, and no interventions are studied to prevent major bleed.

Gregory Castelli, PharmD, FCCP, BCPS, BC-ADM, CDCES
UPMC St. Margaret FMRP, Pittsburgh, PA

The authors declare no conflicts of interest.

Is the etonogestrel implant less effective in preventing pregnancy in patients with a body mass index over 30?

EVIDENCE-BASED ANSWER

Probably not. Limited evidence indicates the etonogestrel implant has similar efficacy in preventing pregnancies in patients with a body mass index (BMI) more than 30 kg/m^2 compared with patients with a normal BMI (SOR: **C**, underpowered cohort studies).

DOI 10.1097/EBP.0000000000001951

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

A 2012 prospective cohort study (n=8,445) examined contraceptive failure rates in patients who were normal weight, overweight, or obese and chose either an etonogestrel implant or a levonorgestrel intrauterine device (LNG IUD) as long-acting reversible contraception (LARC).[1] Through a project to promote use of LARC, researchers offered LARC to 8,445 patients, of which 1,168 consented to the etonogestrel implant and 4,200 consented to the LNG IUD which were provided at no cost. Patients were 14 to 45 years old, sexually active with male partners, without tubal ligation or hysterectomy, not desiring pregnancy in the next year, and not using contraception or interested in changing contraceptive method at the time of enrollment. Of the patients choosing the etonogestrel implant, 37% were normal weight (body mass index [BMI] <25 kg/m^2), 28% were overweight (BMI 25 to <30 kg/m^2), and 35% were obese (BMI ≥30 kg/m^2). In the normal weight group, the mean age was 22 years old and 64% were nulliparous compared with 23 years old and 44% nulliparity in the overweight group and 24 years old and 37% nulliparity in the obese group. Patients were followed for three years with standardized surveys at three months, six months, and then every six months to capture any cases of contraception failure. They were also encouraged to contact the clinic for possible pregnancy, which would be followed up with a pregnancy test at the clinic. Over three years, there was only one pregnancy among the entire cohort, and this patient had a BMI of 30.7 kg/m^2. The failure rate in the obese group was 0.23 per 100 woman-years which was stated as not significantly different than the failure rate of 0 per 100 woman-years in normal weight and overweight groups (statistical analysis not reported). The researchers acknowledged their study was underpowered to detect small differences in contraceptive failure rates.

A 2018 cohort study (n=787), a follow-up of the study above, examined unintended pregnancy rates during prolonged use of either the etonogestrel implant or the LNG IUD for at least one year beyond the respective Food and Drug Administration (FDA)–approved three-year and five-year durations.[2] The researchers recruited 688 patients from the cohort study above who volunteered and consented to continue their LARC and 99 additional patients from other clinics who were not a part of the previous study. Eligibility for enrollment included ages 18 to 45 years old, sexually active with male partners, not desiring pregnancy in the next 12 months, and willing to continue using their LARC for a minimum of one additional year beyond the FDA-approved duration. The 291 patients using the etonogestrel implant were within three months of the current FDA-approved duration of three years, and 25% were normal weight, 23% were overweight, and 52% were obese using the same BMI criteria as above. Patients were followed every six months for 36 months or until they requested device removal. In addition, as with the previous study, patients were encouraged to call study staff and arrange clinic visits for any possible pregnancy. Of the initial 291 patients, 223 (77%) continued to use their etonogestrel implant for more than four years and 102 (35%) continued the implant for more than five years. No reported pregnancies were observed in the implant group in any of the BMI categories through five years of use. For all implant users, the researchers calculated a one-sided 97.5% confidence interval of 0 to 1.5 failures per 100 woman-years through four years and 0 to 2.7 failures per 100 woman-years through five years. The researchers noted the study was underpowered to detect small differences among the BMI classes. Data for frequency of intercourse, additional

contraceptive use, and presence of comorbidities that affect fertility were collected but not reported. EBP

Palistha Amatya, MBBS
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.

References

1. Xu H, Wade JA, Peipert JF, Zhao Q, Madden T, Secura GM. Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. *Obstet Gynecol*. 2012;120(1):21-26. [STEP 3]
2. McNicholas C, Swor E, Wan L, Peipert JF. Prolonged use of the etonogestrel implant and levonorgestrel intrauterine device: 2 years beyond Food -and Drug Administration-approved duration. *Am J Obstet Gynecol*. 2017;216(6):586.e1-586.e6. [STEP 3]

Influenza vaccine after MI reduces all-cause mortality and cardiovascular death at 12 months

Influenza Vaccination After Myocardial Infarction: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

Fröbert O, Götberg M, Erlinge D, et al. Influenza vaccination after myocardial infarction: A randomized, double-blind, placebo-controlled, multicenter trial. *Circulation*. 2021; 144(18):1476-1484. doi:10.1161/CIRCULATIONAHA.121.057042 DOI 10.1097/EBP.0000000000001944

KEY TAKEAWAY: Influenza vaccine reduces all-cause mortality and cardiovascular death at 12 months among patients with a diagnosis of myocardial infarction (MI).

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFO: Inflammation is a key factor in the progression of atherosclerosis. Multiple factors, including influenza virus, may be associated with the inflammatory process. Previous studies suggested that influenza vaccine might reduce all-cause mortality and cardiovascular death in patients with cardiovascular disease (CVD) such as MI.

PATIENTS: Hospitalized adults who were diagnosed with MI
INTERVENTION: Inactivated influenza vaccine
CONTROL: Placebo

OUTCOME:
Primary outcome Composite of all-cause death, MI, and stent thrombosis
Secondary outcomes All-cause death, cardiovascular death, MI, or stent thrombosis

METHODS BRIEF DESCRIPTION:
- The mean age of patients was 60 years old, with 18% women.
- Hospitalized patients were recruited from 30 centers in eight countries: Sweden, Denmark, Norway, Latvia, the United Kingdom, Czech Republic, Bangladesh, and Australia.
- Men and women older than 18 years who were diagnosed with MI or high-risk stable coronary artery disease (CAD) undergoing angiography or percutaneous coronary intervention (PCI) who had not received an influenza vaccine during the previous 12 months.
- Patients were enrolled during the influenza season.
- Patients were included with:
  - ST-segment elevation MI
  - Non–ST-segment MI
  - Stable CAD and 75 years or older undergoing angiography or PCI with at least one additional risk criterion,
  - Finalized coronary angiography or PCI (not inclusion criterion at the Bangladeshi sites)
- Exclusion criteria:
  - Vaccination during the current influenza season or intent to receive the influenza vaccine during the current influenza season.
  - Severe allergy to eggs or previous allergic reaction to influenza vaccine.
  - Endogenic or iatrogenic immunosuppression.
- In a blinded fashion, patients were randomized to either inactivated influenza vaccine or placebo (0.9% sterile normal saline) within 72 h of hospital admission or an invasive coronary procedure.
- Study nurses who administered vaccines were not blinded to the trial medications.
- All-cause death, MI, or stent thrombosis was measured at 12 months after randomization.
- The outcomes were assessed during a phone interview with patients. Information was obtained from the hospital records if a patient could not be contacted.

INTERVENTION (# IN THE GROUP): 1,272
COMPARISON (# IN THE GROUP): 1,260

FOLLOW-UP PERIOD: 12 months after randomization

RESULTS:

Primary outcome

- Compared with placebo, influenza vaccine was significantly more likely to reduce the primary composite outcome of all-cause mortality, MI, or stent thrombosis (intervention, 7.2% vs placebo, 5.3%; hazard ratio [HR] 0.72; 95% CI, 0.39–0.9; NNT=52).

Secondary outcomes

- Compared with placebo, influenza vaccine was significantly more likely to reduce:
  - All-cause death (intervention 4.9% vs placebo 2.9%; HR 0.59; 95% CI, 0.39–0.89; NNT=50)
  - Cardiovascular death (intervention 4.5% vs placebo 2.7%; HR 0.59; 95% CI, 0.39–0.90; NNT=55).
  - There was no significant difference in the rates of MI or stent thrombosis between the two groups.

LIMITATIONS:

- The trial was stopped early because of the COVID-19 pandemic, leading to a possible exaggeration of the effects of the intervention. Patients enrolled from Bangladesh did not routinely undergo invasive investigation and treatment, thus affecting stent thrombosis assessment.
- Only eight patients with high-risk stable CAD were enrolled, leading to reduced representation of this group of patients.
- Researchers evaluated the effect of influenza vaccine only during influenza season. The results may not be generalizable for different times of the year. EBP

Aya Abdelfattah, MBBCH, MPH
SUNY Upstate Medical University Family Medicine Residency Program, Syracuse, NY

The corresponding author is Aya Abdelfattah, MBBCH, MPH; abdelfay@upstate.edu.
The author declares no conflicts of interest.

A vitamin D a day keeps the ICU away in COVID

PROTECTIVE EFFECT OF VITAMIN D SUPPLEMENTATION ON COVID-19–RELATED INTENSIVE CARE HOSPITALIZATION AND MORTALITY: DEFINITIVE EVIDENCE FROM META-ANALYSIS AND TRIAL SEQUENTIAL ANALYSIS

Argano C, Mallaci Bocchio R, Natoli G, Scibetta S, Lo Monaco M, Corrao S. Protective effect of vitamin D supplementation on COVID-19–related intensive care hospitalization and mortality: Definitive evidence from meta-analysis and trial sequential analysis. Pharmaceuticals (Basel). 2023 Jan 16; 16(1):130. doi: 10.3390/ph16010130. PMID: 36678627; PMCID: PMC9864223. DOI 10.1097/EBP.0000000000001984

KEY TAKEAWAY: Vitamin D supplementation administered to hospitalized patients with Covid-19 symptoms significantly decreases intensive care unit (ICU) admission and possibly reduces mortality.

STUDY DESIGN: Meta-analysis and trial sequential analysis of five randomized control trials (N=1,397).

LEVEL OF EVIDENCE: STEP 1.

BACKGROUND: The Covid-19 pandemic prompted a renewed interest in therapies for viral infection. Vitamin D promotes immune function, reduces inflammation, is widely available, and has few risks, which makes it a good therapeutic candidate. Previous studies evaluating the effectiveness of vitamin D on Covid-19 infection have been inconsistent. This study examined the protective effect of vitamin D supplementation on ICU admission and mortality in adults hospitalized with symptomatic Covid-19 infection.

PATIENTS: Non-ICU hospitalized adults with Covid-19 infection.
INTERVENTION: High-dose vitamin D supplementation.
CONTROL: Low-dose vitamin D, placebo, or no vitamin D supplementation.
OUTCOME: Primary outcome: ICU admission and mortality.

METHODS BRIEF DESCRIPTION:

- Patients' ages ranged from 18 to 80 years, with 46 to 60% male.
- Inclusion criteria: No gender or ethnicity restriction, positive Covid-19 infection, and vitamin D supplementation.
- Exclusion criteria: Vitamin D not administered, no test for Covid-19 performed, no assessment of ICU admission or mortality.
- Patients were followed until hospital discharge, ICU admission, or death during hospitalization.
- Intervention groups received doses of vitamin D ranging from 5,000 to 20,000 international units (IU), whereas control groups were either low doses of vitamin D (1,000–2,000 IU), placebo, or no vitamin D.
- Trial sequential analysis was conducted for each of the primary outcomes to determine if the results were conclusive or needed further study.

INTERVENTION (# IN THE GROUP): 797.
COMPARISON (# IN THE GROUP): 600.

FOLLOW-UP PERIODS: eight to 30 days.

RESULTS:

- Vitamin D supplementation had a small-to-moderate effect on reducing ICU admission (5 studies, N=1,397; standardized mean difference [SMD] 0.28; 95% CI, 0.20–0.39; I^2=74%). Trial sequential analysis confirmed this protective effect.
- Vitamin D supplementation moderately reduced mortality (5 studies, N=1,397; SMD 0.49; 95% CI, 0.34–0.72; I^2=49%). However, trial sequential analysis was unable to confirm this association.

LIMITATIONS:

- The effect on ICU admissions was small, and trial sequential analysis indicated that mortality reduction was a false-positive result. EBP

William Read Founds, MD
East Jefferson General Hospital, Metairie, LA

The corresponding author is William Read Founds, MD; William.founds@lcmchealth.org
The author declares no conflicts of interest.

A new option to lower cholesterol without the risks of muscle aches

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N Engl J Med*. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024 DOI 10.1097/EBP.0000000000001994

KEY TAKEAWAY: Bempedoic acid reduces the risk of adverse cardiovascular events compared with placebo and may be an alternative for statin-intolerant patients.

STUDY DESIGN: Double-blind, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BACKGROUND: Bempedoic acid is an ATP citrate lyase inhibitor, which reduces hepatic cholesterol synthesis and increases LDL receptor expression. Unlike statins, this medication is activated in the liver and not in peripheral tissues, so there is theoretically less risk for myalgias.
PATIENTS: Statin-intolerant patients
INTERVENTION: Bempedoic acid
CONTROL: Placebo
OUTCOME: Composite of major adverse cardiovascular events (death, nonfatal MI, nonfatal CVA, coronary revascularization)

METHODS BRIEF DESCRIPTION:

- The study was performed in 32 countries at 1,250 different sites.
- At the start of the study, the mean LDL was 139 mg/dL and the median CRP was 2.3 mg/L.

- Eligible patients entered a four-week run-in period during which they received a single-blind placebo.
- The patients, investigators, and data analysts were masked.
- Inclusion Criteria:
  - Eligible age range was 18 to 85 years old.
  - History of a cardiovascular event (30% of participants) or clinical features suggestive of the need for primary prevention of a cardiovascular event (70% of participants). Specific primary prevention clinical features were not outlined in this trial.
  - Self-reported unable/unwilling to receive statins because of a side effect that occurred while taking a statin or improved after discontinuing a statin.
  - Patients taking other lipid-lowering agents that are not statins were permitted to enroll in the study and take these in combination with bempedoic acid.
- Randomization:
  - Patients were randomly assigned 180 mg of bempedoic acid or placebo in a 1:1 ratio once they completed the run-in period.
  - If a patient had an LDL that was 25% above the baseline at six months, then they were counseled on additional lifestyle modifications.
  - If a patient was taking other lipid-lowering agents and remained above baseline on repeat testing, then their other agents' doses could be adjusted.
- Efficacy analyses were by intention-to-treat.

INTERVENTION (# IN THE GROUP): 6,992

COMPARISON (# IN THE GROUP): 6,978

FOLLOW UP PERIOD: 41 months

RESULTS:

- The bempedoic acid group had fewer primary adverse events compared with placebo (11.7% vs 13.3%; HR 0.87; 95% CI, 0.79–0.96; NNT=63).
- Myalgias were reported in 5.6% of the bempedoic acid group compared with 6.8% in the placebo group. *P* values and 95% CI were not provided.
- Other side effects included an increase in hepatic enzyme levels, an increase in BUN and creatinine, an increase in gout, and an increase in the incidence of cholelithiasis compared with placebo. *P* values and 95% CI were not provided.

LIMITATIONS:

- The trial population were patients who had reported they were unwilling to take a statin because of the risk of side effects or unable to take statins because of a history of side effects, so the mean LDL was high at baseline.
- Bempedoic acid was compared with a placebo and not with a statin.
- Some patients were taking additional lipid-lowering medications. More studies may be needed to determine whether bempedoic acid can be used as a primary lipid-lowering agent. EBP

Ian Smith, MD
UP Health Systems Marquette Family Medicine Residency, Marquette, MI

The corresponding author is Ian Smith, MD; Ian.smith@mghs.org
The author declares no conflicts of interest.

In adults with depression, does regular exercise improve functional outcomes more than psychotropic medication use?

EVIDENCE-BASED ANSWER

Exercise is as effective as pharmacotherapy in improving depressive symptoms (SOR: **A**, systematic review with meta-analysis of randomized controlled trials [RCTs]), as well as improving quality of life, and function (SOR: **C**, small RCTs). Like oral medications, exercise programs may have high drop out rates by six months (SOR: **A**, meta-analysis of RCTs and additional RCT).

DOI 10.1097/EBP.0000000000001891

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

A 2013 Cochrane systematic review and meta-analysis included a subgroup analysis of four randomized controlled trials (RCTs; N=300) that compared exercise (30 minutes walking or jogging 3 times per week) with pharmacotherapy (sertraline 50–200 mg) for treatment of depression in adults.[1] Average patient ages ranged from 52 to 74 years old, and the patients were predominantly female (67%) and Caucasian (76%). Inclusion criterion was RCT study type, and exclusion criteria were studies with combination interventions or those addressing dysthymia or postnatal depression. The primary end points included depressive symptoms, mental quality of life, and physical quality of life using a variety of validated clinical scales. Secondary end points included acceptability of treatment and adverse events. Outcomes were assessed at 4 to 10 months of follow-up. Compared with pharmacotherapy, exercise resulted in no difference in depressive symptoms (4 studies, N=300); standard mean difference (SMD) –0.11 (95% CI, –0.34 to 0.12; I^2=0%), no difference in mental quality of life (1 study, N=25; SMD –11.9; 95% CI, –24.04 to 0.24), no difference in physical quality of life (1 study, N=25; SMD 1.3; 95% CI, –0.67 to 3.27), and no difference in acceptability and completion of treatment (3 studies, N=278; risk ratio [RR] 0.98; 95% CI, 0.86–1.12; I^2=61.09%). The exercise group suffered musculoskeletal injuries in one study (6% in exercise group, not reported in pharmacotherapy group). The pharmacotherapy group reported diarrhea in one study (31% in pharmacotherapy group vs 15% in exercise group; *P*=.03), fatigue in one study (20% in pharmacotherapy group vs 2.4% in exercise group; *P*=.025), and sexual problems in one study (26% in pharmacotherapy group vs 2.4% in exercise group; *P*=.005). Lack of blinding may have biased results toward efficacy of exercise. Results may not be generalizable to younger adults, males, non-Caucasians, or other types and frequencies of exercise interventions.

A 2021 RCT (N=313) compared exercise with pharmacotherapy for treatment of depression in older adults from 10 family medicine clinics in Albacete, Spain during February 2017 to March 2019.[2] The average patient age was 63 years old. Baseline characteristics were similar between study groups, and patients were predominantly female (79%), from lower socioeconomic groups (84%), who reported moderate or intense level of baseline physical activity. Inclusion criteria were active mild-to-moderate depressive episode (by International Classification of Diseases-10 criteria and score of ≥10 on Montgomery–Åsberg Depression Rating Scale [MADRS]). Exclusion criteria were physical or mental limitations preventing participation, contraindications for physical exercise, depression interfering with social or occupational functioning, psychotic symptoms, suicidal ideation, or current use of antidepressants. Patients were randomized to exercise (two 1-hour supervised aerobic, strength, flexibility, and balance sessions per week alongside education to achieve 30 minutes of moderate exercise at home daily) or antidepressant therapy (drug choice at discretion of general practitioner, including SSRIs and heterocyclic or tetracyclic antidepressants). Primary endpoints included improvement in mood to achieve absence of depression on the 0- to 60-point MADRS (includes difficulty concentration and everyday activities, with higher scores being worse) and improvement in self-perceived quality of life on the 0- to 100-point EuroQol EQ-5D

instrument (includes mobility, self-care, performance in usual activities, and pain, with lower scores being worse). Secondary end points included discontinuation of treatment and adverse events. Outcomes were assessed at one-, three-, and six-month follow-up. Compared with pharmacotherapy, exercise resulted in no difference in improvement of depressive symptoms at one month (RR 0.89; 95% CI, 0.71–1.1) and less improvement at three months (RR 0.75; 95% CI, 0.61–0.93) and six months (RR 0.66; 95% CI, 0.5–0.87) in the intention-to-treat analysis; however, exercise resulted in no difference at three months (RR 0.96; 95% CI, 0.82–1.11) and six months (RR 0.95; 95% CI, 0.81–1.11) in the per-protocol analysis. Outcomes were not affected by sex, age, initial level of physical activity, or clinic site. The exercise group had a higher discontinuation rate at three months (39.2% vs 22.6%; *P* not given) and six months (58.2% vs 40%; *P* not given). The exercise group had fewer adverse events than the pharmacotherapy group (8.9% vs 22.5%; *P*=.007); these included musculoskeletal pain, mild contusions, dizziness, syncope, and radial fractures after fall. Reported low attendance at supervised exercise sessions may have diminished efficacy of exercise. Limitations included the discrepancy between the results of intention-to-treat and per-protocol analyses. Lack of blinding may have biased results toward efficacy of exercise, and results may not be generalizable to younger adults. EBP

Pooja Saigal, MD
Nadia Ali, DO
The University of Chicago (NorthShore), Chicago, IL

The corresponding author is Pooja Saigal; poojasaigalmd@gmail.com

The authors declare no conflicts of interest.

References

1. Cooney GM, Dwan K, Greig CA, et al. Exercise for depression. *Cochrane Database Syst Rev*. 2013; 2013: CD004366. [STEP 1]
2. Hidalgo JLT, Sotos JR; DEP-EXERCISE Group. Effectiveness of physical exercise in older adults with mild to moderate depression. *Ann Fam Med*. 2021; 19(4):302–309. [STEP 2]

Have ketosis diets been shown to provide sustained weight loss?

EVIDENCE-BASED ANSWER

In carefully selected and monitored patients, following a very low–calorie ketogenic diet (VLCKD) can lead to 10 to 21 kg of weight loss maintained up to two years, 7 kg more weight loss than with a low-calorie diet (LCD). (SOR: **B**, systematic review and meta-analysis of randomized controlled trials [RCTs], prospective cohort studies, and retrospective cohort study). This diet has multiple contraindications, which may limit its use in everyday practice.

DOI 10.1097/EBP.0000000000001977

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

A 2021 systematic review and meta-analysis of randomized controlled trials (RCTs) and cohort studies (15 studies; N=817) evaluated the effectiveness of a very low–calorie ketogenic diet (VLCKD) for obesity management.[2] Researchers included adults who were overweight or obese (based on body mass index [BMI]), with or without comorbidities. Owing to safety concerns, a VLCKD is generally contraindicated in patients who are or intend to become pregnant; are breastfeeding; or have type 1 diabetes mellitus, hepatic or renal insufficiency, gout, or drug abuse (including alcohol). The studied VLCKD had to consist of three phases: a ketogenic stage lasting up to 12 weeks incorporating calorie and carbohydrate restrictions (ie, <700–800 kcal/day, <13–25% of total calories from carbohydrate), a metabolic stabilization phase where calories were increased (ie, 800–1,500 kcal/day), and a maintenance stage with a return to a balanced diet of 1,500 to 2,250 kcal/day. Patients in the ketogenic phase received micronutrient supplements. The control diet included various other LCDs. The primary outcome was

change in body weight and BMI from baseline to up to 24 months. Compared with control groups, a VLCKD was associated with more weight loss (mean difference [MD] –7.1 kg; 95% CI, –11 to –3.0 kg) and a larger BMI reduction (MD –2.5 kg/m^2; 95% CI, –3.9 to –1.0 kg/m^2). Patients on a VLCKD lost an average of 21 kg (95% CI, –28 to –15) at one year of follow-up. The included studies reported mild side effects of dehydration, transient hypoglycemia, halitosis, gastrointestinal disturbances, hyperuricemia, and transient lipid profile changes, with no incidence data reported. Rare side effects included hypoproteinemia, hypocalcemia or bone damage, hair loss, urolithiasis, and gallstones. Most studies were observational, had limited inclusion of women, had short (<1 year) follow-up, used variable protocols for VLCKD, and provided limited safety data.

A 2020 systematic review and meta-analysis (12 studies; N=801) of RCTs and cohort studies evaluated the efficacy and safety of a VLCKD.[1] Seven of the studies were also included in the above 2021 review. Patients were mostly adults (1 study included patients as young as 14 years old) who were overweight or obese. Researchers excluded patients with the same general contraindications for the VLCKD described above, and diet protocols were similar. Researchers separately analyzed studies with a ketogenic phase of less than or greater than four weeks. The comparison was either a LCD or a very low–calorie diet. The primary outcome was the change in body weight from baseline, with follow-up ranging from three weeks to two years. A VLCKD resulted in weight loss of 10 kg (95% CI –13 to –6.8) and 16 kg (95% CI –19 to –12) in studies with ketogenic phases of less than and greater than four weeks, respectively. This was more than the weight loss in the LCD group but similar to the loss in the very low–calorie group. Discontinuation rates were similar between VLCKD and comparison groups. Limitations of the study were similar to the above 2020 meta-analysis. EBP

Deborah Bross, MD
Torry Pledger, MD
Tyler Wright, MD
John Iskander, MD
Faith Nwokorie, MD
Southern Illinois University—Alton Family Medicine Residency Program, Alton, IL

The corresponding author is Deborah Bross; dbross38@siumed.edu

The authors declare no conflicts of interest.

References

1. Muscogiuri G, El Ghoch M, Colao A, et al. European guidelines for obesity management in adults with a very low-calorie ketogenic diet: a systematic review and meta-analysis. *Obes Facts*. 2021;14(2):222-245. [STEP 1]
2. Castellana M, Conte E, Cignarelli A, et al. Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: a systematic review and meta-analysis. *Rev Endocr Metab Disord*. 2020;21(1):5-16. [STEP 1]

Does chronic inhaled corticosteroid use in adult patients with COPD increase risk of pneumonia?

EVIDENCE-BASED ANSWER

Chronic use of inhaled corticosteroids (ICS) is associated with up to a 40% increase in risk for developing pneumonia in adults older than 40 years with COPD. As a class, higher doses of ICS increased risk by 30% compared with lower doses. Patients using ICS longer than six months, and those with very severe COPD have the greatest risk of developing pneumonia (SOR A, large multistudy meta-analysis of randomized controlled trials and guideline). Pneumonia risk varies based on fluticasone propionate and fluticasone furoate; but not with budesonide, even at high doses (SOR A, large meta-analysis).

DOI 10.1097/EBP.0000000000001978

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

A 2021 meta-analysis of 59 randomized controlled trials (RCTs) (N=103,477) evaluated the risk of developing pneumonia in patients using all types of inhaled corticosteroids (ICSs).[1] The trials included adults (40 years old or older) with stable, moderate to very severe COPD with exclusion of asthma, bronchiectasis, and pulmonary fibrosis. Patients were randomized to receive an ICS (varying formulations and dosages) or non-ICS (control). The primary outcome measured was the incidence of pneumonia, identified when the trial reported its occurrence as an adverse event based on the Medical Dictionary for Regulatory Activities pneumonia-related preferred terms. ICS and non-ICS treatment groups were followed between 3 and 36 months, with a mean of 8.9 months. ICS use resulted in an increased risk of pneumonia (59 trials, odds ratio [OR] 1.4; 95% CI, 1.3–1.5). Subgroup analysis found an increase with all types of ICS: fluticasone (OR 1.47; 95% CI, 1.36–1.59), budesonide (OR, 1.24; 95% CI, 1.05–1.47), mometasone (OR 1.62; 95% CI, 1.05–2.49), and beclomethasone (OR 1.43; 95% CI, 1.03–1.97). A dose-dependent relationship between ICS dose and pneumonia risk was also demonstrated: low dose (27 trials, N=32,592; OR 1.3; 95% CI, 1.2–1.5), medium dose (26 trials, N=27,302; OR 1.5; 95% CI, 1.3–1.8), and high dose (23 trials, N=54,287; OR 1.6; 95% CI, 1.5–1.9). Pneumonia risk was greater with long-term (>6 month) use compared with short-term (<6 month) use (OR 1.4; 95% CI, 1.3–1.6 vs OR 1.3; 95% CI, 1.0–1.6, respectively). ICS treatment increased the risk of pneumonia in all severity subgroups of COPD (moderate COPD: OR 1.3; 95% CI, 1.1–1.4; severe COPD: OR 1.5; 95% CI, 1.4–1.7; very severe COPD: OR 2.5; 95% CI, 1.9–3.4). Pneumonia risk was similarly increased with ICS treatment in patients younger than 65 years old (OR 1.4; 95% CI, 1.3–1.6) and those older than 65 years old (OR 1.4; 95% CI, 1.3–1.5), as well as with those with a BMI less than 25 (OR 1.5; 95% CI, 1.0–2.1) and greater than 25 (OR 1.4; 95% CI, 1.3–1.6). Limitations included that none of the RCTs were specifically designed to monitor pneumonia events, making the studies susceptible to under-reporting. The incidence of pneumonia in the control group would likely have been under-reported as well, possibly mitigating this limitation.

A 2020 meta-analysis of 18 RCTs (N=49,828), many included in the previous meta-analysis, evaluated the risk of pneumonia with ICS use.[2] Inclusion and exclusion criteria and primary outcome of pneumonia risk were the same as the previous meta-analysis. Pneumonia risk was greater with fluticasone propionate (FP) use than with fluticasone furoate (FF) use (relative risk [RR] 1.8; 95% CI, 1.5–2.2 vs RR 1.4, 95% CI, 1.2–1.5, respectively). Fluticasone propionate, fluticasone furoate, and budesonide were further investigated in subgroup analysis. Both high-dose (1,000 mg daily) and low-dose (500 mg daily) fluticasone propionate increased pneumonia risk (RR 1.6; 95% CI, 1.4–1.9; and RR 1.8; 95% CI, 1.2–2.8, respectively). Dosing also seemed to alter the risk of pneumonia using fluticasone furoate (200 mg daily: RR 1.9; 95% CI, 1.3,-2.9; 100 mg daily: RR 1.4; 95% CI, 1.2–1.6; and 50 mg daily: RR 1.6, 95% CI, 1.0–2.4). Neither high-dose (800 mg daily) nor low-dose (400 mg daily) budesonide demonstrated an elevated pneumonia risk. Again, none of the studies evaluated pneumonia as the primary outcome. Studies also lacked statistical analyses of confounding factors such as comorbid conditions and pneumonia severity.

The 2023 Global Initiative for Chronic Obstructive Lung Disease Report released guidelines recommending caution using ICSs in patients with COPD, citing evidence that regular treatment with ICS increases risk for pneumonia, especially in patients with severe disease.[3] ICS treatment was recommended for patients with moderate-to-severe COPD if they have a history of hospitalization(s) for COPD, ≥2 moderate exacerbations per year, eosinophilia >300 cells/μL, or concomitant asthma or a history of asthma. The guidelines specifically discouraged ICS use for patients with repeated pneumonia episodes, low serum eosinophil counts (<100 cells/μL), or a history of mycobacterial infection. EBP

Keeley Hobart, MD
Corey Jones, DO
Tina Jacob, MD
Texas Tech University Health Science Center Family Medicine Residency Program Lubbock, TX

The corresponding author is Dr. Keeley Hobart MD; keeley.hobart@ttuhsc.edu
The authors declare no conflicts of interest.

References

1. Chen H, Sun J, Huang Q, et al. Inhaled corticosteroids and the pneumonia risk in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials. *Front Pharmacol*. 2021; 12: 691621. [STEP 1]
2. Zhang Q, Li S, Zhou W, Yang X, Li J, Cao J. Risk of pneumonia with different inhaled corticosteroids in COPD patients: a meta-analysis *COPD.* 2020; 17:462–469. [STEP 1]

3. Summary of the updated Global Initiative for Chronic Obstructive Lung disease 2023 report. Global Strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease 2023. 74-75. https://goldcopd.org/2023-gold-report-2/. [STEP 2]

What are effective interventions for recurrent yeast vaginitis?

EVIDENCE-BASED ANSWER

For patients with recurrent vulvovaginal candidiasis (VVC), treatment with oral or topical azoles for a duration of six months decreases the risk of clinical recurrence by 64% when compared with placebo (SOR: **B**, meta-analysis of low grade of evidence randomized controlled trials [RCTs]). For patients with recurrent VVC treatment with oteseconazole versus placebo for 13 weeks decreases culture-verified recurrence over 50 weeks with a number needed to treat of three. (SOR: **B**, RCT). Practice guidelines recommend weekly doses of oral fluconazole for six months for suppression of recurrent VVC, acknowledging that topical treatments can be used for patients who cannot or will not take fluconazole (SOR: **C**, practice guidelines).

DOI 10.1097/EBP.0000000000002003

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

A 2022 systematic review and meta-analysis of treatments for recurrent vulvovaginal candidiasis (VVC) examined six randomized controlled trials (RCTs) (N=607) comparing pharmacological treatments with placebo and three RCTs (N=206) comparing oral with topical drug treatments.[1] The review included healthy nonpregnant female outpatients (mean ages ranged from 28 to 37 years) with an acute episode of VVC and a history of recurrent VVC (defined by 4 documented episodes in a 12-month period). In studies comparing a medication with placebo, interventions included fluconazole 150 mg oral weekly, itraconazole 400 mg oral monthly (during menses), ketoconazole 400 mg oral for five days per menstrual cycle, ketoconazole 100 mg oral daily, and clotrimazole 500 mg vaginally once after menstruation. In studies comparing oral versus topical therapies, interventions included fluconazole 150 mg oral either weekly or monthly (during menses), itraconazole 200 mg oral either twice weekly or monthly (during menses), vaginal nystatin 20,000 u for 14 days per month, and vaginal clotrimazole (200 mg twice weekly, 5 g twice weekly, or 500 mg monthly during menses). All treatments were continued for six months, and patients were followed for an additional six months after treatment. Primary outcomes included the proportion of patients with at least one clinical recurrence of VVC during the treatment or follow-up periods. Pharmacologic treatment for recurrent VVC decreased clinical recurrence at six months (6 RCTs, N=607; risk ratio [RR] 0.36; 95% CI, 0.21–0.63; number needed to treat [NNT]=2) and 12 months (6 RCTs, N=585; RR 0.80; 95% CI, 0.72–0.89; NNT=6) compared with placebo. There were no significant differences in VVC recurrence rates between oral and topical therapies at six months (3 RCTs, N=206; RR 1.7; 95% CI, 0.83–3.3) and at 12 months (3 RCTs, N=206; RR 0.95; 95% CI, 0.71–1.3). Adverse event rates were low for both treatment and placebo groups, but it was not possible to pool these data due to variability in reporting. Limitations included heterogeneity of the studies and industry funding. The authors rated the studies as low grade of evidence and with high risk of bias.

A double-blind RCT (n=219) evaluated the efficacy and safety of oteseconazole compared with placebo in the prevention of recurrent culture-verified acute VVC episodes through 50 weeks.[2] Patients were women (mean age 35 years) with a history of recurrent VVC, defined as three or more episodes within 12 months. The intervention group (N=147) received oral oteseconazole 600 mg on day one and 450 mg on day two for the treatment of an acute episode of VVC; those with clinical resolution at two weeks (N=123) took 150 mg oteseconazole oral weekly for 11 weeks (maintenance therapy). The control group (N=72) received oral fluconazole 150 mg on days 1, 4, and 7 as initial treatment; those with clinical resolution at two weeks (N=62) took placebo for 11 weeks. The primary outcome was one episode of culture-verified VVC within the total 50 weeks of study duration. In the intention-to-treat analysis (N=219), oteseconazole was deemed noninferior to fluconazole for resolving acute VVC (93.2% vs 95.8%, respectively). During the maintenance phase through 50 weeks, 5.1% (95% CI, 4.1–6.8) of patients who received

oteseconazole had a recurrent episode of VVC compared with 42.2% (95% CI, 40.3–45.8) of those given placebo (NNT=3). Overall, adverse event rates were similar in both groups: 54% for patients in the intervention group versus 64% in the control group. Most adverse events in each group were mild or moderate.

The 2021 Centers for Disease Control and Prevention (CDC) guideline for the treatment of sexually transmitted infections discussed the use of azole medications for recurrent VVC based on systematic literature review and expert opinion.[3] The guideline recommended 7 to 14 days of topical therapy or an oral dose of 100 mg, 150 mg, or 200 mg of fluconazole on days 1, 4, and 7 to attempt mycologic remission, followed by maintenance antifungal regimen of oral fluconazole (ie, dose of 100 mg, 150.mg, or 200 mg dose) weekly for six months (no SOR or evidence grade provided). The guidelines recommended topical treatments used intermittently if oral suppression was not possible. Several authors of the CDC guideline had funding sources from pharmacologic companies.

The 2020 ACOG guideline on vaginitis in nonpregnant patients discussed the treatment of recurrent VVC based on a systematic literature review and expert opinion.[4] The guideline recommended extended antifungal treatment to decrease the possibility of persistent symptoms (level A recommendation based on good and consistent scientific evidence). The guideline stated that antifungal treatment with oral fluconazole (150 mg weekly for 6 months) controlled more than 90% of recurrent symptomatic episodes. For patients unable or unwilling to take oral fluconazole, the guideline suggested prolonged therapy with intermittent topical agents, such as clotrimazole (500 mg weekly or 200 mg twice a week). No risk of bias was reported by the authors. EBP

Eve Barker, MD
Nikole Shepherdson, DO
Emma Wright, MD
WWAMI Network Faculty Development Fellowship, Seattle, WA

The corresponding author is Emma Wright, MD; emma.wright@mso.umt.edu

The authors declare no conflicts of interest.

References

1. Cooke G, Watson C, Deckx L, Pirotta M, Smith J, van Driel ML. Treatment for recurrent VVC (thrush). *Cochrane Database Syst Rev*. 2022; 1(1):CD009151. [STEP 2]
2. Martens MG, Maximos B, Degenhardt T, et al. Phase 3 study evaluating the safety and efficacy of oteseconazole in the treatment of recurrent VVC and acute VVC infections. *Am J Obstet Gynecol*. 2022; 227(6): 880.e1–880.e11. [STEP 3].
3. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021; 70(4):1–187. [STEP 5]
4. Vaginitis in nonpregnant patients: ACOG practice bulletin, number 215. *Obstet Gynecol*. 2020;135(1):e1–e17. [STEP 5]

Comparing screening for gestational diabetes mellitus, does the one-step or two-step approach lead to improved maternal and newborn outcomes?

EVIDENCE-BASED ANSWER

The one-step method does not lead to improved maternal and newborn outcomes compared with the two-step method (SOR **A**, systematic meta-analysis, evidence-based practice guidelines). However, with one-step compared with two-step screening, patients were nearly two times as likely to be diagnosed with gestational diabetes mellitus (GDM) and receive antidiabetic medications (SOR: **A**, systematic meta-analysis). Guidelines note that the one-step approach may increase the prevalence of GDM and healthcare costs without significantly improving maternal or neonatal outcomes (SOR: **C**, evidence-based and consensus-based guidelines).

DOI 10.1097/EBP.0000000000002002

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

In 2022, a meta-analysis of four RCTs (N=24,966) and 13 observational studies (N=710,677) compared short-

term maternal and neonatal outcomes using the International Association of the Diabetes and Pregnancy Study Groups' one-step (2-hour, fasting 75 g oral glucose tolerance test [OGTT]) versus the Carpenter-Coustan's two-step (50 g nonfasting oral glucose load test, followed by a 100 g fasting OGTT if abnormal) criteria for gestational diabetes mellitus (GDM).[1] The review only included pregnant patients who had no preexisting diabetes and were between 18 and 45 years old. Patients either received the one-step or two-step GDM screening between 24 and 28 weeks of gestational age. The primary outcome was the rate of large for gestational age (LGA) neonates. Secondary outcomes included the number patients diagnosed with GDM and treated with antidiabetic medications, as well as rates of hypertensive disorders, primary cesarean deliveries, fetal macrosomia, shoulder dystocias, neonatal intensive care unit (NICU) admissions, and neonatal hypoglycemia episodes. In the pooled analysis of the RCTs, the rates of LGA neonates were similar with one-step or two-step screening (4 RCTs, N=23,142; risk ratio [RR] 0.95; 95% CI, 0.88–1.0). However, with one-step compared with two step screening, patients were more likely to be diagnosed with GDM (4 RCTs, N=23,412; 16.3% vs 8.3%; RR 2.1; 95% CI, 1.6–2.8; number needed to screen [NNS]=13) and receive medication (3 RCTs, N=23,551; 7.1% vs 3.8%; RR 2.2; 95% CI, 1.2–4.2; NNS=31). Neonates whose mothers had one-step versus two-step screening had higher NICU admission rates (2 RCTs, N=23,192; 5.1% vs 4.5%; RR 1.1; 95% CI, 1.0–1.3; NNS=167) and hypoglycemia (3 RCTs, N=23,471; 9.3% vs 7.6%; RR 1.2; 95% CI, 1.1–1.3; NNS=59). There were no significant differences in other secondary outcomes. Meta-analyses of data from observational trials demonstrated lower rates of LGA infants with one-step versus two-step screening (12 trials, N=700,058; 9.7% vs 10.3%; RR 0.93; 95% CI, 0.9–0.96; NNS=167); however, when researchers analyzed only high-quality studies, the difference in LGA rates between one-step and two-step screening was smaller (3 trials, N=327,984; 10.8% vs 11.1%; RR 0.97; 95% CI, 0.95–0.99; NNS=333). Limitations included the lack of outcome data on preterm birth rates, which could have helped identify differences in hypertensive disorders of pregnancy and respiratory distress syndrome for observational studies and moderate to high heterogeneity among studies in some of the meta-analyses.

A 2023 evidence-based and consensus-based guideline from the American Diabetes Association on the classification and diagnosis of diabetes examined the pros and cons of one-step versus two-step strategies for screening for GDM between 24 and 28 weeks of gestation.[2] The guideline noted that the one-step method might identify additional patients at risk for developing prediabetes and type 2 diabetes later in life and offspring who may have an increased risk of abnormal glucose metabolism and adiposity. However, the one-step approach could lead to an increase in the prevalence of GDM and the medicalization of pregnancy without clear evidence of benefit. The guideline commented that experts disagreed on the optimal strategy and as such made no recommendations for the preferred screening strategy.

In 2021 the U.S. Preventive Services Task Force recommended screening all asymptomatic pregnant persons for GDM starting at 24 weeks of gestation, based on a systematic review of fair or good-quality prospective studies (B recommendation: moderate certainty that there is a moderate net benefit to screening).[3] The authors identified five RCTs comparing one-step with two-step screening strategies and found that although a one-step strategy found more cases of GDM, there were no differences in pregnancy or fetal outcomes, including rates of preeclampsia, hypertensive disorders of pregnancy, preterm delivery, LGA infants, birth injury, neonatal hypoglycemia, or perinatal mortality.

A 2018 evidence-based and consensus-based practice bulletin from the American College of Obstetricians and Gynecologists (ACOG) recommended all pregnant women be screened for GDM, generally between 24 and 28 weeks of gestation (B-level recommendation based on limited or inconsistent scientific evidence).[4] The ACOG bulletin supported the two-step process based on a systematic review and a consensus report indicating that adoption of a one-step approach would likely increase healthcare costs without clinically significant improvements in maternal or newborn outcomes; however, they acknowledged that some practices and institutions might choose to use the one-step process depending on the population served (no strength of recommendation or evidence level provided). EBP

Andrew Wei, MD
Sarah Waterman, MD
Kelsey Motanic, MD
WWAMI Network Faculty Development Fellowship, Seattle, WA

The corresponding author is Andrew Wei; andrew.l.wei@kp.org
The authors declare no conflicts of interest.

References

1. Brady M, Hensel DM, Paul R, et al. One-step compared with two-step gestational diabetes screening and pregnancy outcomes: a systematic review and meta-analysis. *Obstet Gynecol*. 2022; 140(5):712–723. [STEP 1]
2. ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and diagnosis of diabetes: standards of care in diabetes-2023 [published correction appears in Diabetes Care. 2023; 46(5):1106]. *Diabetes Care*. 2023; 46(Suppl 1): S19–S40. [STEP 5]
3. US Preventive Services Task Force, Davidson KW, Barry MJ, et al. Screening for gestational diabetes: US Preventive Services Task Force recommendation statement [published correction appears in JAMA. 2021;326(13):1331]. *JAMA*. 2021; 326(6):531–538. [STEP 2]
4. Gestational diabetes mellitus. ACOG Practice Bulletin No. 190. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2018;131:e49–e64. [STEP 5]

Are primary care providers able to effectively use motivational interviewing techniques in clinic?

EVIDENCE-BASED ANSWER

Motivational interviewing by primary care providers for patients with type 2 diabetes may produce small benefits in multiple patient outcomes, including HbA1c, total cholesterol, blood pressure, body mass index, and physical activity (SOR: **C**, systematic review with low-quality evidence). Undergoing training for motivational interviewing may improve confidence in this technique but results in less than half of providers incorporating it into their practice 30 days after training (SOR: **C**, prospective, single-arm trial).

DOI 10.1097/EBP.0000000000002004

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

A 2017 systematic review (N=1,930) analyzed six studies, which examined the effects of motivational interviewing on type 2 diabetes.[1] The studies consisted of five randomized controlled trials (RCTs) and one trial without control groups. They included data on 181 primary care providers and 97 practices. Five of the studies performed motivational interview training (duration ranging from a single 3-hour session to a 3-day session with 2 half-day follow-ups). One of the studies did not mention whether training was provided. Motivational interviews were carried out in both outpatient and telehealth appointments. Time allotments ranged from 15 minutes to 45 minutes each. Frequency and the number of appointments varied between the studies. Of the six studies included, four found unquantified improvements in at least one patient outcome, which included body mass index, waist circumference, blood pressure, total cholesterol, low-density lipoproteins, fasting blood glucose, HbA1c, and physical activity. Most primary care providers (PCPs) who underwent motivational interview training were partially satisfied with the quality of the training program and motivational interviewing methods. Data gathered one year after the training found that most PCPs reported using specific motivational interviewing methods in their regular practice. None of the studies explored barriers to implementing the technique in practice. Limitations of this systematic review included large heterogeneity and scarcity of details regarding the training techniques used in each study and lack of standardized evaluation tools. In addition, only positive or negative effects of each intervention were reported without citation of any study data, limiting determination of clinical or statistical relevance.

A 2021 prospective, single-arm trial (n=209) involved training PCPs in motivational interviewing.[2] The study included health professionals and health professions students who were primarily female (80%, n=165) and white/non-Hispanic (89%, n=183). Only 11% (n=22) were physicians. Motivational interview training was completed with volunteers in a single training module lasting one to three hours. Researchers provided surveys immediately post training and at 30-day follow-up on the impact the training had on participants' self-reported confidence with patient interactions and perceived importance of the training. No baseline data were collected. Of note, 199 additional participants completed training and

posttraining surveys, but were lost to 30-day follow-up. The researchers reported no statistical difference in immediate posttraining responses between those completing and those lost to 30-day follow-up, leading to the removal of these participants completely from their final assessment. Posttraining, 96% of participants reported both confidence to perform and belief in the importance of motivational interviewing. Ninety-two percent of participants intended to incorporate motivational interviewing in their practice after posttraining, but only 49% (43% decrease, $P<.0001$) reported that they had implemented the motivational interviewing approach at the 30-day follow-up. Confidence to implement (84%, $P<.0001$) and attitudes regarding the overall importance of motivational interviewing (87%, $P=.002$) also decreased to a lesser degree at 30-day follow-up. This study was limited by low-quality design without a comparison group; lack of baseline data; reliance on subjective self-reported data; the brief nature of the training; and the small number of enrolled physicians. EBP

Adriana Carpenter, DO
Kristin Greer, MD
Nellis Family Medicine Residency, Nellis AFB, NV

The corresponding author is Adriana Carpenter; adriana.m.carpenter.mil@health.mil

The authors declare no conflicts of interest.

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

References

1. Thepwongsa I, Muthukumar R, Kessomboon P. Motivational interviewing by general practitioners for type 2 diabetes patients: a systematic review. *Fam Pract*. 2017; 34(4): 376–383. [STEP 2]
2. Hershberger PJ, Martensen LS, Crawford TN, Bricker DA. Promoting motivational interviewing in primary care: more than intention. *Fam Pract*. 2021; 5:7. [STEP 4]

In patients with suspected appendicitis, what is the diagnostic accuracy of ultrasound?

EVIDENCE-BASED ANSWER

In children, adolescents, and nonpregnant adults with suspected appendicitis, ultrasound (US) has an estimated sensitivity of 77% and specificity of 60% (SOR: **A**, single meta-analysis). The American College of Radiology (ACR) recommends US as an alternative initial imaging option for nonpregnant adults and as a primary initial imaging option for pregnant adults and children with suspected appendicitis (SOR: **C**, consensus guidelines).

DOI 10.1097/EBP.0000000000001883

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

A 2021 meta-analysis of 18 studies (N=4,209) attempted to correlate the diagnostic accuracy of abdominal ultrasound for appendicitis in all age groups compared with histopathology.[1] The review included retrospective, prospective, or cross-sectional studies conducted between 2010 and March 2021. Histopathology reports served as the reference standard in this meta-analysis, with studies using other imaging modalities (computed tomography [CT] or magnetic resonance imaging [MRI]), gross surgical diagnosis, or other primary reference standards excluded. Studies encompassed all age groups and included complete data to allow for pooled statistical analysis. Patients were children and nonpregnant adolescents and adults one to 89 years old. Overall sensitivity of

abdominal US in acute appendicitis was 77% (95% confidence interval [CI], 75%–79%), and overall specificity was 60% (95% CI, 58%–62%). The likelihood ratio of a positive test was 2.6 (95% CI, 1.6–4.4), and the likelihood ratio of a negative test was 0.45 (95% CI, 0.28–0.74). Sources of heterogeneity between the studies included disproportion of female patients, a low number of prospective studies, varying types of ultrasound probes used, and variable ultrasonographer experience level. Two of the trials were rated as high risk of bias; however, the other 16 studies were rated as low risk.

The 2022 ACR Appropriateness Criteria for initial imaging in right lower quadrant pain rated various imaging modalities as "usually appropriate," "may be appropriate," or "usually not appropriate" for diagnosis of appendicitis.[2] Experts made recommendations based on the assumption that the imaging study was performed by an expert and not by nonradiologist physicians trained on ultrasound. An US of the abdomen or pelvis was rated as "may be appropriate" in adults with suspected appendicitis. CT abdomen and pelvis with intravenous (IV) contrast was the only imaging modality more highly recommended and was rated as "usually appropriate" for all nonpregnant adults. In pregnant adults, MRI abdomen and pelvis without IV contrast or US abdomen were rated as "usually appropriate."

In children, the 2018 ACR Appropriateness Criteria rated US as a "usually appropriate" initial imaging modality in cases of suspected acute appendicitis with intermediate clinical risk, recommending it above all other imaging modalities.[3] EBP

William Dente Ellis, DO
Michelle Swenson, DO
Nellis Family Medicine Residency, Nellis AFB, NV

The corresponding author is William Dente Ellis, DO; William.s.ellis36.mil@health.mil

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 U.S. Air Force at large, or the Department of Defense.

References

1. Fu J, Zhou X, Chen L, Lu S. Abdominal ultrasound and its diagnostic accuracy in diagnosing acute appendicitis: a meta-analysis. *Front Surg.* 2021;8:707160. [STEP 1]
2. Expert Panel on Gastrointestinal Imaging, Kambadakone AR, Santillan CS, et al. ACR Appropriateness Criteria® right lower quadrant pain: 2022 update. *J Am Coll Radiol.* 2022;19(11):S445-S461. [STEP 4]
3. Expert Panel on Pediatric Imaging, Koberlein GC, Trout AT, et al. ACR Appropriateness Criteria® suspected appendicitis-child. *J Am Coll Radiol.* 2019;16(5S):S252-S263. [STEP 4]

Does hair dye use increase the risk of breast cancer?

EVIDENCE-BASED ANSWER

Permanent hair dye and rinse usage are associated with an increased breast cancer risk (SOR: **B**, meta-analysis of observational studies). However, no dose-dependent association between hair dye usage and breast cancer incidence has been identified (SOR: **C**, large prospective cohort study).

DOI 10.1097/EBP.0000000000001952

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

A 2020 meta-analysis of 14 case-control and prospective cohort studies (n=210,319) evaluated breast cancer risk.[1] Female patients with a mean age of 53 years old were recruited from multiple countries, including the United States, China, Finland, Canada, Iran, and Australia. Patients were included if they reported exposure to hair care products. Exclusion criteria included case reports, conference papers, and non-English studies. Patients who used different types of hair treatments such as permanent hair dye (defined as penetrate the hair cuticle and alters the structure and color), semipermanent hair dye (defined as covering hair shaft with slight penetration and last approximately 6–8 weeks), straighteners (defined as chemicals penetrating the hair shaft to disrupt disulfide bonds to straighten curls), and rinse users (defined as temporary hair dye covering hair shaft without penetration lasting a couple of washes) were compared with patients with natural hair. Breast cancer occurrence was self-reported. There was a significant association between hair dye usage and breast cancer occurrence (12 studies, N=91,593; odds ratio [OR] 1.07; 95% CI,

1.01–1.13). With regard to different types of hair treatments, permanent hair dye (7 studies, N=199,537; OR 1.08; 95% CI, 1.03–1.14) and rinse treatment (6 studies, N=81,133; OR 1.17; 95% CI, 1.02–1.35) had significant associations with breast cancer occurrence, but semipermanent hair dyes (6 studies, N=81,133; OR 1.09; 95% CI, 0.92–1.28) and straighteners (2 studies, N=50,994; OR 1.04; 95% CI, 0.96–1.14) did not. Limitations included variations in chemical formulation of dyes, cancer diagnosis that was not collaborated by medical records or pathology reports, unmeasured confounding factors such as overweight and parity, and a high risk for selection and publication bias.

A 2020 prospective cohort study (n=117,200) examined the association between personal use of permanent hair dyes and breast cancer incidence among female nurses in the United States.[2] Nurses were 96% White with a mean age of 42.9 years old. Researchers excluded patients with no information on exposure to hair dyes or with a cancer diagnosis at baseline. Cancer incidence was self-reported. The incidence was confirmed by review of medical records and pathology reports or by linkage to state cancer registries. No significant association was observed between any natural hair color and breast cancer incidence (HR 1.02; 95% CI, 0.98–1.07). Among nurses with any hair color, there was no significant association between cumulative dose of permanent hair dye use and breast cancer incidence: 1 to 99 times (HR 1.01; 95% CI, 0.96–1.06), 100–199 times (HR 0.99; 95% CI, 0.92–1.06), and >200 times (HR 1.09; 95% CI, 1.02–1.16). Limitations included nonexperimental design with a predominately White sample. In addition, nurses might be more adept at taking precautions while applying the dyes compared with the general population. EBP

Susie Wenstrup, MD
Kiranpreet Dhaliwal, DO
Harjinder Sidhu, MD
Valley Family Medicine Residency, Modesto, CA

The corresponding author is Susie Wenstrup, MD; swenstrup@schsa.org
The authors declare no conflicts of interest.

References

1. Xu S, Wang H, Liu Y, et al. Hair chemicals may increase breast cancer risk: a meta-analysis of 210319 subjects from 14 studies. *PLoS One*. 2021; 16(2):e0243792. [STEP 1]
2. Zhang Y, Birmann BM, Han J, et al. Personal use of permanent hair dyes and cancer risk and mortality in US women: prospective cohort study. *BMJ*. 2020; 370:m2942. [STEP 2]

Is practicing yoga an effective alternative treatment for anxiety?

EVIDENCE-BASED ANSWER

Maybe. There is a small, short-term positive effect of yoga on anxiety levels compared with no treatment, but no significant effect on patients with DSM-diagnosed anxiety disorders (SOR: **B**, meta-analysis of low-quality, randomized, controlled trials [RCTs]). Patients who practice more hours of yoga and with higher anxiety at the beginning of practice have more reduction of anxiety symptoms (SOR: **B**, meta-analysis of low quality RCTs). Learning yoga may reduce self-reported anxiety symptoms in yoga-naive college students (SOR: **C**, small RCT).

DOI 10.1097/EBP.0000000000001913

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

A 2018 systematic review and meta-analysis compared the effectiveness of yoga practice to reduce anxiety levels in patients with self-reported increased anxiety symptoms or anxiety disorders (8 international randomized controlled trials [RCTs]; N=319).[1] Patients were diagnosed by Diagnostic and Statistical Manual (DSM), International Classification of Disease (ICD) 10, or validated clinician-based or self-report anxiety symptoms questionnaires. Mean ages ranged from 30 to 39 years. Two of the studies were removed from the meta-analysis because they did not have enough raw data for analysis (n=70). Intervention groups included group or individual multicomponent yoga, posture-based yoga, and breathing- or meditation-based yoga. Patients with cointerventions such as pharmacotherapy were eligible if all groups

received the same cointervention. Outcomes were assessed at 12 weeks, six months, and 12 months after randomization using the State-Trait Anxiety Inventory or the Taylor's manifest anxiety scale. Meta-analysis showed a small, short-term, positive effect of yoga on anxiety levels compared with no treatment (3 studies, N=162; standardized mean difference [SMD] –0.43; 95% CI, –0.74 to –0.11). Somewhat paradoxically, there was a large effect from yoga compared with other active interventions like relaxation (3 studies, N=79; SMD –0.86; 95% CI, –1.6 to –0.15), although the number of patients was small. There were no statistically significant effects of yoga on patients with DSM-diagnosed anxiety disorders. Limitations to this review included the variety of diagnoses in the overarching term "anxiety," heterogeneous interventions, a high risk of selection bias, and a lack of blinding.

A 2016 meta-analysis of 17 trials compared the effect of Hatha yoga (meditation, breathing exercises, and physical postures, the most common yoga practiced in United States) on self-reported anxiety (17 RCT; N=501).[2] Eleven studies used waitlist controls; patients were 75% female with a mean age of 41 years old. There was no overlap with the 2018 systematic review because this meta-analysis included only Hatha yoga. Studies were excluded if yoga was administered in conjunction with another treatment or if the yoga practice was only one component of Hatha yoga. The mean intervention frequency was 2 times per week with a duration of nine weeks. Initial patient anxiety symptoms and postintervention outcomes were assessed using the State-Trait Anxiety Inventory or Beck Anxiety Inventory. The intervention group had a small increased improvement in anxiety scores over controls (Hedges' g 0.44; 95% CI 0.25–0.63). Higher number of hours of practice and sessions per week were associated with greater benefits, especially in participants with clinically elevated anxiety levels compared with those without elevated anxiety. There was a medium improvement in anxiety in the active intervention group compared with waitlist or no treatment (Hedges' g 0.61; 95% CI, 0.25–0.98). This analysis was limited by the low number of studies, which made it difficult to examine specific anxiety disorders. Trials were at high risk of bias with unclear sequence generation, allocation concealment, and incomplete outcomes.

A 2016 RCT compared the effectiveness of mindfulness compared with Hatha yoga and a noninterventional control group on coping with psychological disorders in yoga-naive college students older than 18 years experiencing symptoms of depression or anxiety (N=90).[3] This study was not included in either of the above meta-analyses because it focused on yoga-naive students and included a meditation group in addition to a control group. All groups continued medication (57%) and/or psychotherapy (22%) if already started. Patients were excluded if physical disability prevented practice of gentle yoga; they had been diagnosed with a thought disorder, bipolar disorder, or borderline personality disorder; they engaged in active substance use or had pending legal dispositions. Students were not assigned to groups based on mood diagnosis. Each intervention group completed 75-minute training sessions per week for eight weeks and were encouraged to practice the learned modalities 20 min a day outside of class. The Hamilton Anxiety Scale and the Student-Life Stress Inventory were collected before intervention and at weeks 4, 8, and 12. Twenty-one students reported anxiety only (31%), 39 students reported depression and anxiety (58%), and 7 students reported depression only (10%). The dropout rate was 26% and was the same among the groups. There was a significant decrease of 32% (n=23 yoga students; $P<.01$) on the Hamilton Anxiety Scale from pre to post study for those in the yoga group. In addition, participants were noted to state, "I am more positive about life," "I am more accepting of my situation," "I am calmer and happier," and "I am more fulfilled with everyday life". Limitations of the study included the population being mostly Caucasian women. EBP

Deidre Gubac, BS
Krystal Foster, MD
University of Missouri, Columbia, MO

The Corresponding Author is Krystal Foster, FosterKry@health.missouri.edu

The authors declare no conflicts of interest.

References

1. Cramer H, Lauche R, Anheyer D, et al. Yoga for anxiety: a systematic review and meta-analysis of randomized controlled trials. *Depress Anxiety*. 2018; 35(9):830–843. [STEP 2]
2. Hofmann SG, Andreoli G, Carpenter JK, Curtiss J. Effect of Hatha yoga on anxiety: a meta-analysis. *J Evid Based Med*. 2016; 9(3):116–124. [STEP 2]
3. Falsafi N. A randomized controlled trial of mindfulness versus yoga: effects on depression and/or anxiety in college students. *J Am Psychiatr Nurses Assoc*. 2016; 22(6):483–497. [STEP 2]

Does infection with COVID-19 in pregnant women increase the risk of developing preeclampsia?

EVIDENCE-BASED ANSWER

Yes, the odds of developing preeclampsia in pregnant women infected with COVID-19 are 60% to 100% higher than those not infected (SOR: **B**, meta-analysis of cohort studies and multiple individual cohort studies). Furthermore, there is weak evidence to suggest that increased severity of COVID-19 illness correlates to a dose–response relationship between subsequent development of preeclampsia (SOR: **C**, observational study).

DOI 10.1097/EBP.0000000000001895

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

A 2022 systematic review and meta-analysis included 14 prospective cohort studies, 12 retrospective cohort studies, and two cross-sectional studies (N=790,954) and evaluated the association between SARS-CoV-2 infection during pregnancy and the incidence of preeclampsia.[1] Studies included pregnant patients with a current or previous diagnosis of SARS-CoV-2 infection at any stage of gestation (N=15,524). SARS-CoV-2 was diagnosed through RT-PCR in 18 studies, antigen tests in three studies, and serum antibody testing in three studies. The remaining four studies diagnosed based on laboratory tests or clinical signs and symptoms of COVID-19. Most patients were diagnosed with infection during the third trimester. The primary outcome was the development of preeclampsia. Secondary outcomes included preeclampsia with severe features, preeclampsia without severe features, eclampsia and HELLP syndrome. All but one study found that the frequency of preeclampsia was higher among pregnant patients with a diagnosis of SARS-CoV-2 (pooled unadjusted odds ratio [OR] 1.6; 95% CI, 1.5–18; pooled adjusted odds ratio [aOR] 1.6; 95% CI, 1.4–1.8). Among secondary outcomes, SARS-CoV-2 infection increased the odds of developing preeclampsia with severe features (OR 1.76; 95% CI, 1.2–2.6), eclampsia (OR 1.97; 95% CI, 1.0–3.8), and HELLP syndrome (OR 2.1; 95% CI, 1.5–2.97) compared with pregnant patients without infection. SARS-CoV-2 infection conferred a greater risk of developing preeclampsia when diagnosed before 32 weeks of gestation (hazard ratio [HR] 2.9; 95% CI, 1.2–6.9). Both asymptomatic (OR 1.6; 95% CI, 1.2–2.1) and symptomatic (OR 2.1; 95% CI, 1.6–2.8) SARS-CoV-2 infections increased the odds of preeclampsia.

A 2021 prospective, multinational, cohort study evaluated the effect of COVID-19 on maternal and neonatal outcomes.[2] The study included 706 adult women with a diagnosis of COVID-19 and 1,424 controls. Live born, stillborn, singleton, and multiple gestation pregnancies were included in this study and those with congenital anomalies. Women and neonates were excluded from the study if their data were previously published. COVID-19 was diagnosed by laboratory confirmation, radiographic pulmonary findings suggestive of COVID-19, or two or more predefined COVID-19 symptoms. Preeclampsia was a secondary outcome and part of the primary outcome of maternal morbidity and mortality index. Infection with COVID-19 conferred a greater risk of developing preeclampsia or eclampsia (relative risk [RR] 1.8; 95% CI, 1.3–2.4). Of the patients in the study with a diagnosis of COVID-19, 59% were symptomatic. The risk of developing preeclampsia, eclampsia, or HELLP syndrome was greater in both symptomatic (RR 2.0; 95% CI, 1.3–2.99) and asymptomatic (RR 1.6; 95% CI, 1.01–2.6) patients with COVID-19.

A 2021 retrospective observational study (N=1,223) assessed for a dose–response relationship between severity of SARS-CoV-2 infection and the likelihood of preeclampsia.[3] Data were gathered from 14 different National Health Service maternity hospitals in the United Kingdom on pregnant women with SARS-CoV-2 infection diagnosed by PCR. Patients were categorized into four groups: (1) asymptomatic, (2) mild illness (individuals with various signs and symptoms of COVID-19 but did not have shortness of breath, dyspnea, or abnormal chest imaging), (3) moderate illness (individuals with lower respiratory disease on clinical assessment or imaging with oxygen saturation >94%

on room air), and (4) severe illness (individuals who required high dependency or intensive care secondary to respiratory impairment/failure or multiorgan dysfunction). The primary outcome was the occurrence of preeclampsia in patients exposed to SARS-CoV-2. The observed rate of preeclampsia among those diagnosed with COVID-19 was higher for all exposed groups compared with the expected population. The baseline cohort risk of preeclampsia was approximately 1% compared with rates of incidence of 1.9% in the asymptomatic group, 2.2% in the mild illness group, 5.7% in the moderate illness group, and 11.1% in the severe illness group (chi-square test for trend; $P=.0017$). Severe COVID-19 disease was associated with the highest risk of preeclampsia (adjusted relative risk [aRR] 4.9; 95% CI, 1.6–15). There was a higher risk of preeclampsia with moderate or severe COVID-19 diagnosis as compared with asymptomatic or mild disease (aRR 3.3; 95% CI, 1.5–7.4). EBP

Paige Macky, CPT, MD
Andrew Jones, CPT, MD
Justin Wilkie, MD
Dwight D. Eisenhower Army Medical Center Family Medicine Residency Program, Fort Gordon, GA

The corresponding author is Justin Wilkie; Justin.l.wilkie2.civ@health.mil

The authors declare no conflicts of interest.

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

References

1. Conde-Agudelo A, Romero R. SARS-COV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis. *Am J Obstet Gynecol.* 2022; 226(1): 68–89.e3. [STEP 1]
2. Villar J, Ariff S, Gunier RB, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID multinational cohort study. *JAMA Pediatr.* 2021; 175(8):817–826. [STEP 3]
3. Lai J, Romero R, Tarca AL, et al. SARS-CoV-2 and the subsequent development of preeclampsia and preterm birth: evidence of a dose-response relationship supporting causality. *Am J Obstet Gynecol*. 2021; 225(6):689–693.e1. [STEP 3]

Does screening for Adverse Childhood Experiences in pediatric patients increase referrals to community services or engagement with behavioral health services compared to no screening?

EVIDENCE-BASED ANSWER

Screening for adverse childhood experiences (ACEs) may result in a 2.5-fold and a 17-fold higher rate of referrals for substance use and intimate partner violence, respectively, as well as a doubling in community services enrollment at 12-month follow-up (SOR: **C**, systematic review of a quasiexperimental study and an randomized controlled trial with high risk of bias). ACE screening within large integrated healthcare systems may increase the rate of completed behavioral health visits by 750% (SOR: **C**, retrospective cohort study).

DOI 10.1097/EBP.0000000000001901

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

A 2022 systematic review identified one randomized controlled trial (RCT) (N=336) and one quasiexperimental study (N=1,165) evaluating the effects of screening for adverse childhood experiences (ACEs) in children on rates of referral to community services.[1] In the RCT, the children had a mean age of 2.5 months old, 81% had Medicaid insurance, and reported ethnicity was 44% Black, 24% White, and 23% Hispanic. The RCT screened for maternal depression (using the Personal Health Questionnaire) and asked mothers about their own education

level, employment, childcare needs, housing, food security, and household heat as part of a routine well-child visit; patients with positive screening tests (not defined) were offered a referral to a community service. The RCT reported improved referral rates of 70% for the intervention group versus 8% for the control group (adjusted odds ratio [aOR] 30; 95% CI, 15–60) and when followed up at 12 months, more mothers were enrolled in community services in the intervention than in the control group (39% vs 24%; aOR 2.1; 95% CI, 1.2–3.7). In the quasiexperimental study, 85% had Medicaid insurance and reported that ethnicity was 37% Black, 42% White, and 15% other; age data were not available. The quasiexperimental study used trained personnel visiting the patient's home to ask mothers about depression, substance use, and intimate partner violence using standardized questionnaires and followed up with motivational interviewing and referral to community resources. The quasiexperimental study showed higher referral rates to community services for patients who screened positive for substance use (OR 17; 95% CI, 2–138) and intimate partner violence (OR 2.5; 95% CI, 1.3–4.9) but not for maternal depression (OR 1.1; 95% CI, 0.72–1.7); however, there was significant deviation from the study protocol in that only 32% of patients who screened positive for ACEs were offered referrals. The RCT was deemed to be at high risk of bias because of the lack of blinding for the patients and providers, and the quasiexperimental study had high risk of bias because of confounding variables and missing data. No studies reported mental health outcomes, and none measured potential harms of screening.

A 2022 retrospective cohort study assessed the rate of successful engagement with behavioral health services for children and adolescents (n=4,030), using a pilot intervention of ACE screening and referral.[2] The researchers extracted data from electronic medical records of patients in an integrated healthcare system in Southern California that served more than 4.7 million people, including 1.5 million children. Patients had a mean age of 10 years (range 2–18 years), 51% were female, and reported race/ethnicity was 73% Hispanic, 14% Black, 6% White, 4% Asian/Pacific islander, and 4% other or unknown; 33% had Medicaid insurance. The comparator was usual care (ie, the system that existed prior to the intervention), which consisted of administering a screening questionnaire of 10 pertinent ACEs (eg, exposure to physical, emotional, or sexual abuse, feeling neglected, abandoned, or unloved, and living with a parent or adult who was mentally ill, using illicit substances, or had a history of incarceration). Providers referred patients with positive scores, defined as more than four positive items or three items plus behavioral symptoms, directly to behavioral health services. The intervention screening tool consisted of a 17-item questionnaire encompassing the same 10 ACE items as the prestudy questionnaire, as well as seven questions assessing exposure to violence in the community, discrimination, housing instability, food insecurity, and separation from parent or guardian because of foster care, immigration, illness, or death. The intervention also included a direct referral from the healthcare provider to a medical social worker as well as a "warm handoff" (ie, direct connection) from the social worker to behavioral health services after the assessment of appropriateness. Patients were referred if they had more than one positive answer on the screening questionnaire and accompanying behavioral or mental health symptoms. The outcome was the rate of completed visits to behavioral health services within 90 days after a positive ACE screen. This rate increased from 4.3% preintervention to 32.5% postintervention (incidence rate ratio 7.5; 95% CI, 1.5–36.2). The study was limited by the lack of information about referral services provided outside of the integrated healthcare system and whether the care delivered reduced mental health symptoms. EBP

Matthew Acosta, MD
Esta Lai, MD
Nicolle Siegart, MD
Megan Wilson, MD
University of Washington Family Medicine Residency Program, Seattle, WA

The corresponding author is Megan Wilson; mlwilson@uw.edu
The authors declare no conflicts of interest.

References

1. Loveday S, Hall T, Constable L, et al. Screening for adverse childhood experiences in children: a systematic review. *Pediatrics*. 2022; 149(2):e2021051884. [STEP 2]
2. Negriff S, DiGangi MJ, Sidell M, Liu J, Coleman KJ. Assessment of screening for adverse childhood experiences and receipt of behavioral health services among children and adolescents. *JAMA Netw Open*. 2022; 5(12):e2247421. [STEP 4]

How much do oral NSAIDs increase bleeding risk in patients on anticoagulation therapy?

EVIDENCE-BASED ANSWER

NSAID use while on anticoagulation therapy significantly increases risk of major bleeding and clinically relevant nonmajor bleeding compared with anticoagulation therapy alone (SOR: **A**, multiple randomized controlled trial [RCT]s), as well as increasing rates of stroke and systemic embolism (SOR: **B**, single RCT), and gastrointestinal bleeding risk (SOR: **B**, retrospective cohort).

DOI 10.1097/EBP.0000000000001930

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

A 2020 randomized controlled trial (RCT) (N=18,201) assessed the risk of major and clinically relevant nonmajor (CRNM) bleeding in patients with atrial fibrillation (AF) on oral anticoagulation with concomitant NSAID use.[1] NSAID use included ibuprofen, diclofenac, naproxen, meloxicam, and celecoxib irrespective of dose. Patients were randomly assigned to three groups: baseline NSAID use (n=832), incident NSAID use during the trial (n=2,185), and never use (n=14,406). NSAID dosage information was not provided. Across the three groups, patients had a similar median age of 70 years and were 35% to 37% female. Patients with prosthetic heart valves, aspirin use (>165 mg daily), clopidogrel use, stroke within seven days of randomization, severe kidney disease (creatinine clearance <30 mL/min), and chronic liver disease were excluded. The primary outcome was major bleeding defined as acute or subacute bleeding with a decrease in hemoglobin of at least two g/dL, transfusion of at least two units of red blood cells, bleeding in a physiologically critical site, or bleeding, resulting in death. The secondary outcomes included CRNM bleeding defined as acute or subacute overt bleeding with none of the major bleeding criteria, but leading to hospitalization, surgical or medical treatment, or a change in antithrombotic therapy. The initiation of NSAIDs during the trial was significantly associated with an increased risk of major bleeding (hazard ratio [HR] 1.6, 95% CI, 1.1–2.3) and CRNM bleeding (HR 1.7, 95% CI, 1.2–2.5). This study was limited by unbalanced sample sizes across the three groups.

A 2018 post hoc analysis of a randomized evaluation of long-term anticoagulant therapy with either dabigatran or warfarin (N=18,113) assessed the risk of major bleeding by comparing patients taking nonselective NSAIDs at least once during the trial (dosage information not presented) with patients who never used NSAIDs during the trial.[2] Patients who used NSAIDs (n=2,279) were an average age of 71.5 years and 61% male, whereas nonusers (n=15,834) were an average age of 71.5 years and 63.9% male. Patients were included from 951 clinical centers in 44 countries with a diagnosis of AF. Patients with severe heart valve disorder, recent or severe stroke, pregnancy, or creatinine clearance <30 mL/min were excluded. The primary outcome was risk of major bleeding defined as hemoglobin reduction of 2.0 g/L, need for transfusion, or symptomatic bleeding. Secondary outcomes included major gastrointestinal bleeding (defined as reduction in hemoglobin level of at least 2.0 g/L, need for at least 2 units of blood or packed cells, or symptomatic bleeding in a critical organ), and stroke (focal neurologic deficit lasting 24 hours or greater, or resulting in death) and systemic embolism (an acute vascular occlusion of the extremities or any organ). Compared with patients who did not use NSAIDs, concomitant NSAID use significantly increased the rate of major bleeding (HR, 1.7; 95% CI, 1.4–2.0), major gastrointestinal bleeding (HR, 1.8; 95% CI, 1.4–2.4), and the rate of stroke or systemic embolism (HR, 1.5, 95% CI, 1.1–2.0).

A 2020 retrospective cohort study (N=41,183) assessed the risk of gastrointestinal bleeding (GIB) associated with oral anticoagulation (OAC) and NSAID use in patients with AF.[3] Data were obtained from the Danish National Patient Registry, which tracked hospital admission and discharge diagnoses, and the National Prescription Registry, which held comprehensive pharmacy data. The median age of patients was 70 years, 55% were male, and 40.6% received a

vitamin K antagonist (VKA), 17.4% apixaban, 13.7% rivaroxaban, and 28.3% dabigatran. Patients were oral anticoagulant-naive adults with a diagnosis of AF who filled a first-time prescription for a VKA, dabigatran, rivaroxaban, or apixaban between August 22, 2011, and June 30, 2017. Patients were excluded if they had a history of valvular disease, total hip or knee arthroplasty within five weeks before inclusion day, pulmonary embolism or deep vein thrombosis within six months before inclusion day, or if they received two prescriptions for different OACs. NSAID exposure was estimated in the form of an average daily dose, which was calculated from prescription data showing the strength of the formulation, number of tablets per day, and length of prescription access. The primary outcome was GIB that was specified as a diagnosis of bleeding gastrointestinal ulcer, hematemesis, melena, or unspecified gastrointestinal bleeding requiring hospitalization. Compared with OAC treatments alone, concurrent NSAID use significantly increased risk of GIB for apixaban (HR, 3.0, 95% CI, 1.5–4.4), VKA (HR, 2.0, 95% CI, 1.2–2.7), dabigatran (HR, 1.5, 95% CI, 0.76–2.3), and rivaroxaban (HR, 1.9, 95% CI, 0.77–3.1). EBP

Felix Morales, MD
Aleksandr Doroshkin, MD
Joshua McGuire, MD
Jared Riley, MD
Texas Tech University Family Medicine Residency Program, Lubbock, TX

Corresponding author: Felix Morales, MD; Felix.Morales@ttuhsc.edu.
The authors declare no conflicts of interest.

References

1. Dalgaard F, Mulder H, Wojdyla DM, et al. Patients with atrial fibrillation taking nonsteroidal anti-inflammatory drugs and oral anticoagulants in the aristotle trial. *Circulation*. 2020; 141(1):10–20. [STEP 2]
2. Kent AP, Brueckmann M, Fraessdorf M, et al. Concomitant oral anticoagulant and nonsteroidal anti-inflammatory drug therapy in patients with atrial fibrillation. *J Am Coll Cardiol*. 2018; 72(3):255–267. [STEP 3]
3. Olsen A-MS, McGettigan P, Gerds TA, et al. Risk of gastrointestinal bleeding associated with oral anticoagulation and non-steroidal anti-inflammatory drugs in patients with atrial fibrillation: a nationwide study. *Eur Heart J Cardiovasc Pharmacother*. 2020; 6(5):292–300. [STEP 3]