May 2024

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

May 2024
Volume 27 | Number 5

EVIDENCE-BASED PRACTICE May 2024 Volume 27 | Number 5

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 27 | NO. 5 | May 2024

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

EBP FEATURES

PURLs

DIVING FOR PURLs

IN DEPTH

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.

EDITORIAL POLICY

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

DISCLOSURE

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.

Albumin versus crystalloids for AKI in the cirrhotic patient

CASE

A 51-year-old woman with history of alcohol use disorder, alcoholic cirrhosis, and chronic pain presents to the emergency department with abdominal distension and three days of nausea and vomiting. She is found to have a creatinine of 2.1 mg/dL from a last recorded creatinine of 0.9 mg/dL two weeks prior. Urine studies suggest that her acute kidney injury is secondary to a prerenal cause, and she is admitted for a trial of hydration. The attending physician wonders if an albumin infusion is more likely to improve her condition than a crystalloid infusion.

DOI 10.1097/EBP.0000000000001863

Bottom Line

Probably not. In fact, cirrhotic patients with acute kidney injury (AKI) receiving crystalloid without albumin have similar outcomes in partial or complete resolution of AKI and improved in-hospital survival (SOR: **B**, retrospective cohort). Although albumin infusions may improve serum creatinine, creatinine clearance, and renal blood flow, the effect is not better than crystalloid (SOR: **C**, disease-oriented outcome).

Review of the Evidence

A 2022 retrospective cohort study evaluated the effectiveness of albumin infusions in 4,126 hospitalized patients with cirrhosis over 18 years old with AKI.[1] Intravenous albumin use was compared with nonuse in these patients to determine a preferred treatment for AKI in cirrhotic patients. If patients received albumin or albumin plus a crystalloid, they were considered albumin users (n=1,207), and if the patients were only given crystalloids, they were considered nonusers (n=2,919). Baseline serum creatinine and daily serum creatinine was collected for each patient every day while hospitalized. Both unmatched and propensity score–matched data were presented. Unmatched results revealed better outcomes in the albumin nonuser group for partial recovery (71% nonusers vs 64% users; $P<.001$), complete recovery (63% nonusers vs 53% users; $P<.001$), and in-hospital survival (93% albumin nonusers vs 76% users; $P<.001$). Propensity-matched results did not find significant differences in outcomes for partial recovery (73% nonusers vs 69% users; $P=.365$) or complete recovery (61% nonusers vs 55% users; $P=.151$) but did find significance for in-hospital survival in favor of albumin nonuse (91% nonusers vs 79% users; $P<.001$). The study was limited by the heterogeneity of albumin dosing (weight-based vs non–weight-based dosing, albumin only given to cirrhotic patients with higher MELD-Na scores, etc).

A 2015 observational study[2] evaluated the effects of albumin infusions on serum creatinine and renal blood flow in 10 adults with acute decompensation of cirrhosis with AKI. Patients were given an intravenous albumin infusion of 40 to 60 g/d for three to four days, and post-intervention measurements were taken the day after the last infusion. These patients had a significant improvement in their creatinine from a mean of 2.4 to 1.7 mg/dL ($P<.01$) and improvement in creatinine clearance from a mean of 13 to 28.3 mL/min ($P<.001$). Renal blood flow also significantly increased from a mean of 277 to 430 mL/min ($P<.001$). This study had significant limitations including a very low number of patients and no comparison group.

CASE CONCLUSION

The patient is monitored and undergoes a therapeutic paracentesis. She is also given a 1-L bolus of likelihood ratio for hydration. The following day, her creatinine shows significant improvement to 1.3 mg/dL. She was tolerating orally at that time and was discharged. EBP

Ryan Richmond, MD
Emily Sue Spencer, MD
University of Colorado (University Hospital) Program (Founding), Aurora, Colorado

The corresponding author is Emily Sue Spencer, MD; EMILY.SPENCER@CUANSCHUTZ.EDU
The authors declare no conflicts of interest.

References

1. Patidar KR, Adibuzzaman M, Naved MA, et al. Practice patterns and outcomes associated with intravenous albumin in patients with cirrhosis and acute kidney injury. *Liver Int*. 2022; 42(1):187–198. [STEP 4]
2. Garcia-Martinez R, Noiret L, Sen S, Mookerjee R, Jalan R. Albumin infusion improves renal blood flow autoregulation in patients with acute decompensation of cirrhosis and acute kidney injury. *Liver Int.* 2015; 35(2): 335–343. [STEP 4]

How not to miss half of occlusion myocardial infarctions

PRACTICE CHANGER

In patients with symptoms suggestive of acute coronary syndrome (ACS), consider occlusion myocardial infarction (OMI) in those with EKGs showing maximal ST depression in leads V1-V4, even if the EKG does not meet ST-elevation MI (STEMI) criteria. In this setting, consider prompt referral for emergent reperfusion therapy.

From this study, it appears that STDmaxV1-4 is a specific predictor of posterolateral OMI and should be treated as OMI.

Strength of Recommendation: B, based on a single retrospective case-control study.

Meyers HP, Bracey A, Lee D, et al. Ischemic ST-Segment Depression Maximal in V1-V4 (Versus V5-V6) of Any Amplitude Is Specific for Occlusion Myocardial Infarction (Versus Nonocclusive Ischemia). J Am Heart Assoc. 2021; 10(23):e022866. doi:10.1161/JAHA.121.022866.

DOI 10.1097/EBP.0000000000002076

Illustrative case

A 58-year-old man presents with two hours of constant chest pressure, shortness of breath, and palpitations that started while walking his dog.[1]

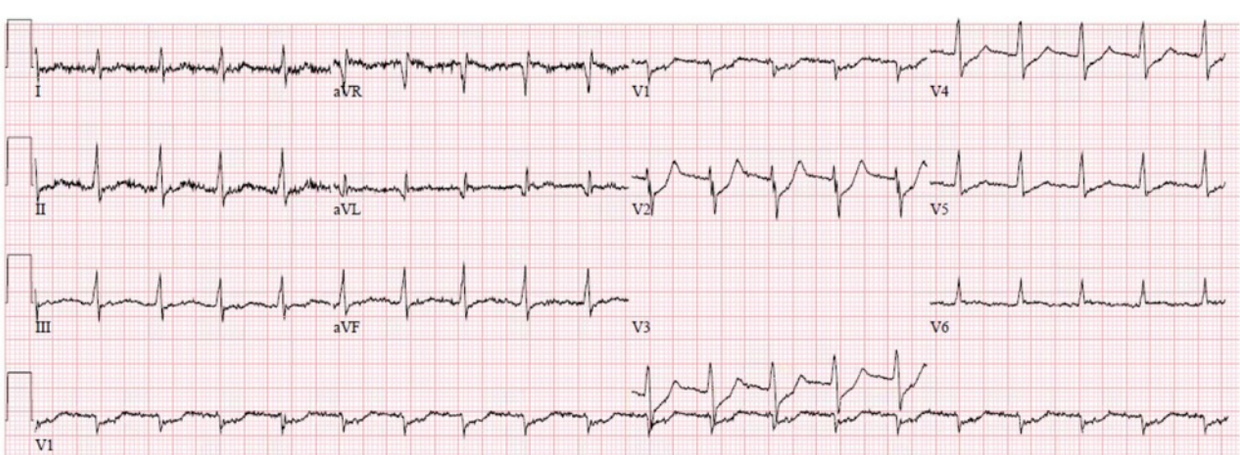
The below EKG is obtained and deemed not to meet STEMI criteria. The patient's chest pain persists, and a repeat EKG is unchanged. Should you advocate for observation or for immediate activation of the cardiac cath lab team?

Clinical context

The term occlusion myocardial infarction describes an acute coronary syndrome in which near or total coronary occlusion in the setting of insufficient collateral circulation causes active infarction.[2] Many OMI are not captured by the ST-segment elevation criteria specified in the Fourth Universal Definition of Myocardial Infarction (STEMI criteria).[3,4] Patients with non–ST-segment elevation MI (NSTEMI) with delayed management of OMI are known to experience increased mortality compared with NSTEMI without OMI.[5]

It is of note that baseline EKGs with a normal QRS have significant baseline (nonischemic) ST-segment elevation (STE) in V2 and V3. In most men, that STE is >1 mm.[6,7] For this reason, any ST-segment depression, even <0.1 mV (1 mm) in V1-V4, is abnormal and suspicious for posterior OMI in the right clinical context,[1] as explained below.

The ST depression (STD) of posterior OMI is reciprocal to an STE vector of subepicardial (transmural) ischemia directed posteriorly. Thus, posterior OMI manifests as STD in precordial leads. However, precordial STD may be attributable to either OMI or subendocardial ischemia. Evidence suggests that the STD of posterior OMI is maximal in V1–V4, whereas the STD of subendocardial ischemia is maximal in V5 and V6.[8,9]



Among OMI not meeting the STEMI criteria, approximately 10% are OMI of the "posterior" wall of the myocardium.[10] These isolated posterior OMI may be attributable to acute occlusion of the left circumflex artery or posterior branches of the right coronary artery.[1] Circumflex occlusions without STE have the same amount of myocardium at risk as those with STE, and the same amount of myocardial salvage is achieved with reperfusion of the occlusion. However, >50% of patients with circumflex occlusion do not receive emergent reperfusion and experience increased mortality.[11]

This study evaluated the diagnostic accuracy of ST-segment depression maximal in leads V1-V4 (STDmaxV1-4) for the identification of OMI.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching Dynamed, UpToDate, ESC guidelines, ACC/AHA 4th Universal Definition of MI, National Cardiovascular Data Registry, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction with the terms *ST depression*, *posterior myocardial infarction*, *ST elevation*, *posterior wall MI* to find additional literature to place this research into the context of current clinical practice.

Study summary

This multisite retrospective case-control study reviewed high-risk populations with ACS (n=808) at two different emergency departments (ED), each with >100,000 ED visits per year. Both hospitals are academic centers and have cardiac catheterization capability. EKG interpretation was performed by two of the study authors, both academic emergency medicine faculty, and included various predefined EKG findings and objective measurements. The EKG interpreters were blinded to all patient information except age and sex (necessary for interpretation of STEMI criteria, which are age-based and sex-based).

The selection of participants, both cases (with OMI) and controls (without OMI), involved accessing the cardiac catheterization laboratory activation database as well as use of a previously collected prospective cohort of ED patients with suspected ACS. To ensure the final cohort contained a substantial number of control patients with abnormal EKGs, additional controls came from a database of patients without OMI but with STE, STD, or T-wave inversion.

The study subjects were separated into known posterolateral OMI (n=265) and noncardiac patients (n=543). A total of 118 patients had suspected ischemic STDmaxV1-4, and of those, 90% had an acute lesion, 84% had an OMI, and 81% underwent percutaneous intervention (PCI). Among these 118 patients, the study found that STDmaxV1-4 had a specificity of 96.5%, sensitivity of 37.4%, and positive likelihood ratio of 10.67 for OMI. In addition, STDmaxV1-4 had a specificity of 96%, sensitivity of 39.7%, and positive likelihood ratio of 9.94 for OMI requiring PCI.

In a subgroup of 99 patients with OMI and STDmaxV1-4, only 47% met STEMI criteria. Among patients with OMI and STDmaxV1-4 as well as STEMI criteria, the emergence of STEMI criteria was delayed by a median of one hour in comparison with STDmaxV1-4. The study patients who were STEMI OMI-negative and STDmaxV1-4 positive were less likely than STEMI-positive patients to receive PCI within 90 minutes.

What's new

In this study, ST-segment depression maximal in leads V1–V4 was found to be an indicator of posterior OMI with 97% specificity. STEMI criteria missed half of OMI detected by STDmaxV1-4. These data support that, in the setting of ACS, STDmaxV1-4 is concerning for posterior OMI until proven otherwise and should prompt consideration of emergent reperfusion therapy even in the absence of STEMI criteria.

In a cohort with high-risk acute coronary syndrome in the emergency department, precordial ischemic ST-segment depression maximal in V1-V4 (rather than V5-V6) had 96% specificity for OMI requiring percutaneous coronary intervention. Expanding OMI criteria to include STDmaxV1-4 will increase the identification of OMI and the likelihood of timely PCI.

Caveats

Resources were not available to execute a prospective, consecutive cohort study. This retrospective case-control study resulted in a study population that was inherently high risk for ACS and may not be generalizable to other ED patients or outpatient primary care patients.

This study was not able to determine the accuracy of STDmaxV1-4 in juxtaposition with posterior lead criteria

because only eight patients in this study had posterior leads placed and recorded.

A significant limitation of this study is that EKG interpretation is subjective. Twenty-nine patients had STDmaxV1-4 classified as "nonischemic," either identified as such by comparison with a baseline EKG or explained by a non-OMI diagnosis such as a right bundle branch block. It is notable that of these 29 patients, 3 had OMI.

Challenges to implementation

Identification of STDmaxV1-4 is subjective and likely requires dedicated training as well as experience to affect clinical practice. This may limit its utility in the average family physician's practice. Even when recognized as possible OMI by the family physician, that physician is not typically activating the cardiac cath lab, let alone performing the coronary angiogram. The physician will need to advocate with other physicians on behalf of their patient, armed with the nuances of this study and AHA guidelines. EBP

Allan Akin, MD
Christopher Choe, MD
Malissa Talbert, MD
University of Tennessee College of Medicine-Chattanooga Family Medicine Residency, Chattanooga, TN

The corresponding author is: Malissa Talbert, MD; malissa.talbert@erlanger.org
The authors declare no conflict of interest.

References

1. Meyers HP, Bracey A, Lee D, et al. Ischemic ST-segment depression maximal in V1-V4 (versus V5-V6) of any amplitude is specific for occlusion myocardial infarction (versus nonocclusive ischemia). *J Am Heart Assoc*. 2021; 10(23): e022866.
2. Meyers HP, Smith SW. News: a new paradigm for AMI management. *Emerg Med News*. 2020; 42(10):1,34.
3. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. *Circulation*. 2018; 138(20):e618–e651.
4. Pendell Meyers H, Bracey A, Lee D, et al. Accuracy of OMI ECG findings versus STEMI criteria for diagnosis of acute coronary occlusion myocardial infarction. *Int J Cardiol Heart vasculature*. 2021; 33:100767.
5. Meyers HP, Bracey A, Lee D, et al. Comparison of the ST-elevation myocardial infarction (STEMI) vs. NSTEMI and occlusion MI (OMI) vs. NOMI paradigms of acute MI. *J Emerg Med*. 2021; 60(3):273–284.
6. Surawicz B, Parikh SR. Prevalence of male and female patterns of early ventricular repolarization in the normal ECG of males and females from childhood to old age. *J Am Coll Cardiol*. 2002; 40(10):1870–1876.
7. Macfarlane PW, Browne D, Devine B, et al. Modification of ACC/ESC criteria for acute myocardial infarction. *J Electrocardiol*. 2004; 37(Suppl):98–103.
8. Shah A, Wagner GS, Green CL, et al. Electrocardiographic differentiation of the ST-segment depression of acute myocardial injury due to the left circumflex artery occlusion from that of myocardial ischemia of nonocclusive etiologies. *Am J Cardiol*. 1997; 80(4):512–513.
9. Mark DB, Hlatky MA, Lee KL, Harrell FE, Califf RM, Pryor DB. Localizing coronary artery obstructions with the exercise treadmill test. *Ann Intern Med*. 1987; 106(1):53–55.
10. Oraii S, Maleki M, Tavakolian AA, Eftekharzadeh M, Kamangar F, Mirhaji P. Prevalence and outcome of ST-segment elevation in posterior electrocardiographic leads during acute myocardial infarction. *J Electrocardiol*. 1999; 32(3):275–278.
11. O'Keefe JH Jr, Sayed-Taha K, Gibson W, Christian TF, Bateman TM, Gibbons RJ. Do patients with left circumflex coronary artery-related acute myocardial infarction without ST-segment elevation benefit from reperfusion therapy? *Am J Cardiol*. 1995; 75(10):718–720.

Brainiac boost—when multivitamins fall short in reducing cognitive delay

Baker LD, Manson JE, Rapp SR, Sesso HD, Gaussoin SA, Shumaker SA, Espeland MA. Effects of cocoa extract and a multivitamin on cognitive function: A randomized clinical trial. *Alzheimers Dement*. 2023;19(4):1308-1319. doi: 10.1002/alz.12767.

DOI 10.1097/EBP.0000000000002098

This randomized, double-blind, placebo-controlled, 2×2 factorial clinical trial explored the impact of cocoa and multivitamins on cognitive function in adults 65 years of age and older. The study enrolled 2,262 English-speaking adults (60% female, 89% non-Hispanic White) without a history of myocardial infarction, stroke, insulin use for diabetes, recent cancer diagnosis, or other serious medical illnesses who were able to complete the baseline telephone cognitive assessment. Patients demonstrated a 75% pill adherence during a two-month placebo run-in period, measured by self-report, after which they were randomly assigned to one of four groups: daily multivitamin (n=551, MVM—Centrum Silver); cocoa extract (n=553, CE) containing 500 mg/day cocoa flavanols, epicatechins, theobromine, and caffeine; a combination of CE and MVM (n=571); or placebo (n=587).

Cognitive assessments were conducted using telephone at baseline and annually over a three-year period. The primary outcome, a global cognition composite, presented as a z-score with higher scores noting improved performance. Secondary outcomes included episodic memory and executive function composites. The battery of included tests comprised the modified Telephone Interview for Global Cognitive Status (TICSm with short and long-delay word list recall), immediate and delayed Story Recall (SRI & II), Oral Trail-Making Test Part B (OTMT-B), Verbal Fluency by category (VF-C) and letter (VF-L), Number Span (NS), and Digit Ordering Test (DOT).

Researchers found a statistically significant improvement in cognitive testing with the use of daily multivitamins (mean z=0.07, 95% CI 0.02–0.12; *P*=.007). However, on a 20-word immediate recall test, the primary endpoint, both groups achieved a mean recall of approximately eight words, with only a 0.2-word improvement in the multivitamin recipients. The daily use of cocoa did not affect global cognition (mean z-score = 0.03, 95% CI: –0.02 to 0.08; *P*=.28). An intention-to-treat analysis was performed, and no other outcome measures reached statistical significance. Significant limitations to this study included a study population not representative of older Americans, reliance on self-report, and the inability to assess which components of the MVM were responsible for the observed effects.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching UptoDate and Dynamed with the terms "multivitamins" and "cognitive decline/Dementia" 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: Multivitamin supplementation is an inexpensive and accessible intervention that showed a statistically significant improvement in cognitive function in older adults. However, the clinical importance of this intervention remains unclear without clinically meaningful improvement in cognitive function compared with placebo.

Mohammed Salih, MD
University of Missouri, Columbia, MO

The Corresponding Faculty Author on the manuscript is: Carl Tunink, tuninkc@health.missouri.edu
The authors declare no conflict of interest.

Atypicals still not typical for treatment-resistant depression

Lenze EJ, Mulsant BH, Roose SP, et al. Antidepressant augmentation versus switch in treatment-resistant geriatric depression. *N Engl J Med* 2023;388(12):1067-1079. doi: 10.1056/NEJMoa2204462.

DOI 10.1097/EBP.0000000000002074

This was a randomized, two-step trial comparing the efficacy of established strategies for treatment-resistant depression in older adults. Adults 60 years

old or older with treatment-resistant major depressive disorder (MDD) (lack of remission from the current episode after two or more adequate trials of antidepressants) were enrolled at five large academic medical centers. Initial threshold for entry was a Patient Health Questionnaire 9 (PHQ-9) score of $\geq$6 (scores range from 0 to 27, higher scores indicate greater severity of symptoms). The inclusion threshold was amended to a PHQ$\geq$10 after the study had been running 18 months. Patients were excluded if they had an inability to consent, dementia, a history of or current psychotic symptoms, high risk of suicide, medication contraindications, unstable medical illness, or substance use disorder.

Patients were on average 69 years old, predominantly female (67%), White identifying, and well-educated (mean 14–15 years of school). In step 1 of the study, patients were randomly assigned in a 1:1:1 ratio to augmentation of their current antidepressant with aripiprazole (N=211), augmentation with bupropion (N=206), or switching to bupropion (N=202). Patients who were nonresponders in step 1 or ineligible on initial review were transitioned to step 2 which compared augmentation with lithium (N=127) versus switching to nortriptyline (N=121). No placebo was used. Patients were followed with calls or in-person visits every other week with a trial clinician who assessed overall depression using the PHQ-9, adherence to medication regimen and possible side effects. Effectiveness of each intervention was evaluated after 10 weeks.

The primary outcome was psychological well-being which was evaluated with the National Institute of Health (NIH) Toolbox Emotion Battery subscales for Positive Affect and General Life Satisfaction (calculated as a combined T score average between the two subscales; normative population mean, 50; higher scores indicating greater well-being). Secondary outcomes included remission from depression on the Montgomery-Asberg DepressionRating Scale (MADRS; range, 0–60, with higher scores indicating greater depression), changes in MADRS score, and changes in social participation and physical function on the Patient-Reported Outcomes Measurement Information Systems (PROMIS, mean T score 50 with higher scores indicating greater participation or function). Safety outcomes included rates of falls and serious adverse events, such as life-threatening illness, hospitalization, disability or permanent damage, and death.

For step 1 patients, augmentation with aripiprazole was statistically more effective in improving psychological well-being than switching to bupropion (difference in change 2.79, 95% CI 2.8–5.9, *P*=.014). The relative risk (RR) of remission in the aripiprazole augmentation group compared with switch to buproprion was 1.5 (95% CI 1.1–2.1) and similar to the risk of remission for bupropion augmentation compared with medication switch (RR 1.49, 95% CI 1.0–2.1). Between the aripiprazole augmentation and bupropion switch groups, the absolute risk reduction was 9.6%, with an NNT=10 to prevent one case of remission. There were fewer falls in the aripiprazole augmentation group compared with the bupropion augmentation group, with a relative risk of 0.59 (95% CI 0.4–0.9, *P*=.02).

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. No additional literature search was conducted.

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

Bottom line: Resistant major depression in adults older than 60 years old is common in the primary care setting. Augmentation with an atypical antipsychotic-like aripiprazole shows promise compared with more commonly used buproprion and had fewer reported adverse outcomes. However, the short follow-up period of the study may underestimate the side-effect profile of atypicals, especially risk of tardative dyskinesia, given the usual duration of therapy required to treat MDD.

Jessica Zha, MD
Roxanne Radi, MD, MPH
Corey Lyon, DO
University of Colorado Family Medicine Residency, Aurora, CO

The corresponding author is Roxanne Radi; Roxanne.Radi@DHHA.org.
The authors declare no conflict of interest.

Combination nasal steroid–decongestant for allergic rhinitis

Kumar RS, Jain MK, Kushwaha JS, et al. Efficacy and Safety of Fluticasone Furoate and Oxymetazoline Nasal Spray: A Novel First Fixed Dose Combination for the Management of Allergic Rhinitis With Nasal Congestion. J Asthma Allergy. 2022;15:783-792. doi:10.2147/JAA.S357288.

DOI 10.1097/EBP.0000000000002058

This multicenter double-blind randomized controlled trial compared a combination of fluticasone furoate and oxymetazoline hydrochloride 27.5/50 μg in a single nasal spray with fluticasone furoate nasal spray 27.5 μg alone in 250 adults 18 to 65 years old having allergic rhinitis with moderate-to-severe nasal congestion. Efficacy was measured using a multisystem validated scale, the Total Symptom Score (TSS). The TSS combines a Total Nasal Symptom Score (TNSS) that comprised congestion, sneezing, itching, and rhinorrhea and Total Ocular Symptom Score (TOSS) that comprised itching/burning, tearing/watering, and redness. Each symptom was scored on a four-point scale. Patients self-administered two sprays in each nostril at night beginning the day of randomization and continuing for 28 days. Evaluation for rebound congestion, rhinitis medicamentosa, or aggravation of other symptoms was performed on day 30. The primary outcome was the reduction in the nighttime TNSS. Secondary outcomes were reduction in the daytime TNSS, nasal congestion score, TSS, TOSS, and the proportion achieving complete relief of nasal congestion both day and night. Nighttime and daytime TNSS scores suggested greater reduction with the combination group compared with monotherapy; however, authors did not provide *P* values. The proportion of complete relief of day and nighttime nasal congestion (day 3: 9.8% vs 1.6%; day 7: 20.3% vs 4.7%; day 14: 29.3% vs 7.9%; day 28: 44.7% vs 26.8%; $P<.05$ all time-points) was greater with combination treatment over monotherapy. No differences within the two groups were reported for other secondary outcomes, adverse events, or worsening of symptoms two days after stopping the treatment (day 30).

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	No
Change in practice	Yes	Clinically meaningful	No

Bottom line: A combined nasal spray of decongestant plus steroid may provide relief of nighttime congestion in patients with allergic rhinitis. However, concerns for validity are introduced with authors only providing data analysis for secondary outcomes and the lack of *P*-values and CIs for the primary outcome.

Marianne Koenig, PharmD
Yufei Ge, MD, MS
UPMC St. Margaret Family Medicine Residency, Pittsburgh, PA

The corresponding author is Yufei Ge; Yufeige@gmail.com.
The authors declare no conflict of interest.

Estrogen products and HTN risk

Citation: Kalenga CZ, Metcalfe A, Robert M, Nerenberg KA, MacRae JM, Ahmed SB. Association between the route of administration and formulation of estrogen therapy and hypertension risk in postmenopausal women: A prospective population-based study. *Hypertension* 2023;80(7):1463-1473. doi:10.1161/HYPERTENSIONAHA.122.19938.

DOI 10.1097/EBP.0000000000002059

This population-based cohort study investigated the association between the method of estrogen hormone therapy and hypertension in postmenopausal women. The study was a data review from Alberta, Canada between 2008 and 2019 assessing the records of women 45 years old and older who filled two or more consecutive prescriptions for hormone therapy over a period of at least six months. Of the 229,636 women who met this criterion, 151,498 used the same pre-

scription for at least six months. Records were excluded if the hormone therapy was <6 months or use was inconsistent. The study then excluded women on progestin-only therapy (15,240) or combined estrogen–progestin therapy (24,018). Only those on estrogen only therapy were included (112,240). Researchers also looked at estrogen formulation as use of estradiol (61,875), conjugated equine estrogen (48,868), and estrone (1,497).

The primary outcome of the study was incident hypertension, defined as two or more physician claims of hypertension over a two-year period or one hypertension recording on hospital discharge after initiation of estrogen therapy. The authors used a Cox proportional hazard model to calculate hazard ratios for hypertension in women using oral hormone therapy compared with nonoral hormone therapy (transdermal, vaginal, or intramuscular). In a total of 112,240 women using hormone therapy, oral estrogen was associated with a higher risk of hypertension compared with both transdermal (hazard ratio [HR] 1.14; 95% CI, 1.08–1.2) and vaginal (HR 1.19; 95% CI, 1.13–1.25) estrogens. Conjugated equine estrogen was associated with an increased risk of hypertension compared with estradiol (HR 1.08; 95% CI, 1.04–1.14) but not estrone (HR 1.0; 95% CI, 0.93–1.1). Duration of estrogen exposure and cumulative dose of estrogen was positively associated with risk of hypertension.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching UpToDate, DynaMed, and USPFTF with the terms "estrogen therapy side effects," "hormone replacement side effects," "risks associated with estrogen replacement," "oral estrogen," and "transdermal estrogen" to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: This study shows a possible link between route of administration of estrogen hormone replacement therapy and hypertension, especially in younger cohorts of women. It may not be translatable given the exclusion of progesterone use. More studies are needed to investigate the link between hormone therapy and estrogen including route. Although a possible risk of hypertension could be considered as decisions for therapy and route decided on with a patient.

Melissa Johnson, MD
Corey Lyon, MD
Department of Family Medicine, University of Colorado, Denver, CO

The corresponding author is Corey Lyon; Corey.Lyon@cuanschutz.edu.

The authors declare no conflict of interest.

Is wearable technology accurate at detecting atrial fibrillation?

EVIDENCE-BASED ANSWER

Yes, wearable technology can accurately detect atrial fibrillation in patients with and without a history of atrial fibrillation (SOR: **A**, meta-analysis of case-control and single cohort study and an observational study). Wearable technology is also able to diagnose atrial fibrillation with 90% sensitivity and 83% specificity among patients who have recently undergone cardiac surgery (SOR: **B**, single cohort study).

DOI 10.1097/EBP.0000000000001995

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

A 2021 meta-analysis of nine studies (case-control and a single cohort study) evaluated wrist-worn wearable devices compared with conventional methods in detecting atrial fibrillation (AF) in adults (N=1,629).[1] The study included patients with and without a history of AF, an average age of 70 years old, and 29% female. Devices included Apple, Samsung, and KardiaBand compared with conventional methods such as 12-lead ECG, telemetry, implantable cardiac monitor, and 7-lead Holter monitoring. Data detailing how long each device was worn were not reported. Among the three devices, no significant difference was observed in sensitivity (Apple devices, 3 studies, N=689; sensitivity [Sn] 98%; 95% CI, 0.96–0.997; KardiaBand, 3 studies, N=324; Sn 97%, 95% CI, 0.945–0.99; Samsung, 3 studies, N=568; Sn 96%; 95% CI, 0.93–0.98; intergroup P=.276). Wrist-worn wearable devices had high sensitivity (9 trials, N=not reported; Sn 97%; 95% CI, 0.96–0.98). However, the specificity (Sp) of the three groups was statistically different (KardiaBand, 3 studies, N=324; Sp 81%; 95% CI, 0.76–0.87; Samsung, 3 studies, N=568; Sp 98%; 95% CI, 0.967–0.99; Apple, 3 studies, N=689; Sp 100%; 95% CI 0.99–1.0; intergroup comparison P<.001). Limitations of this review included indirect comparison between the devices; one study was supported by industry and was not published in a peer-reviewed journal.

Similarly, a 2022 observational study (n=200) determined the feasibility of using a commercial smartwatch for ambulatory monitoring of AF.[2] The study compared Garmin Forerunner 945 smartwatch-derived photoplethysmography (PPG) data with traditional Holter monitoring. Patients went through concurrent Holter monitor and smartwatch use, with Holter monitor readings used to assess the accuracy of PPG data. All patients carried a diagnosis of paroxysmal atrial fibrillation. Excluded patients were younger than 20 years old, pregnant, or unable to wear either device for 24 hours. A duration of an episode of AF was defined as 30 seconds. Overall, PPG data had a Sn of 97%, Sp of 89%, and diagnostic accuracy of 94%. The study was funded by the manufacturer.

Finally, a 2022 correlation study evaluated the accuracy of wearable Apple smartwatches (n=79) with an objective of developing a machine learning algorithm to immediately diagnose AF in cardiac surgery patients in the postoperative period.[3] Patients were 57% male with a mean age of 66 years old and were monitored for average of 13 days. Patients with a permanent pacemaker, sensitivity to wristbands, and those with chronic AF who did not undergo arrhythmia-related surgery were excluded from the study. All patients were given an Apple smartwatch that was reapplied when the patient was discharged from ICU to the general ward after cardiac surgery, with the devices placed in "workout mode" to allow evaluation of HR every five-six seconds. Central ECG monitoring was compared with HR data from watches using PPG, and the machine learning model focused on pulse rate to determine occurrence of AF events. Ultimately, the diagnostic accuracy was 94% for the ROC curve, with Sn of 91% and Sp of 84% for diagnosing AF during the recovery period after heart surgery. Limitations of this study included a small sample size of only 79 patients and periods of missing data from Apple watches during

monitoring because of device removal or technology transferring difficulties. EBP

Jessa Hernandez, MD
Kreena Shah, MD
Rachel Spayd, DO
Sarah Davis, MD
Inspira Mullica Hill Family Medicine Residency, Mullica Hill, NJ

The corresponding author is Sarah Davis; daviss@ihn.org
The authors declare no conflicts of interest.

References

1. Belani S, Wahood W, Hardigan P, et al. Accuracy of detecting atrial fibrillation: a systematic review and meta-analysis of wrist-worn wearable technology. *Cureus*. 2021; 13(12):e20362. [STEP 1]
2. Chang PC, Wen MS, Chou CC, Wang CC, Hung KC. Atrial fibrillation detection using ambulatory smartwatch photoplethysmography and validation with simultaneous holter recording. *Am Heart J*. 2022; 247:55–62. [STEP 2]
3. Hiraoka D, Inui T, Kawakami E, et al. Diagnosis of atrial fibrillation using machine learning with wearable devices after cardiac surgery: algorithm development study. *JMIR Form Res*. 2022; 6(8):e35396. [STEP 2]

Does starting naltrexone in a patient with alcohol use disorder and elevated baseline liver transaminases cause further liver injury compared with acamprosate and gabapentin?

EVIDENCE-BASED ANSWER

Naltrexone does not cause hepatotoxicity in patients with liver enzyme elevation less than 3 times the upper limit of normal. Naltrexone is similarly safe compared with gabapentin or acamprosate and is associated with decreases in baseline aspartate aminotransferase/alanine aminotransferase elevations (SOR: **C**, clinical trials with disease-oriented outcomes).

DOI 10.1097/EBP.0000000000001963

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

A 2008 double-blind, randomized, controlled trial (n=624, 64% male and median age 44 years old) assessed hepatic safety of monthly injectable naltrexone (XR-NTX) in adults with alcohol dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, who also reported ≥2 episodes of heavy drinking (≥5 and ≥4 standard drinks per day for men and women respectively) per week.[1] The researchers measured monthly alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, and bilirubin levels while patients received high (380 mg, n=205) or medium (190 mg, n=210) doses of XR-NTX or placebo injection (n=209) over a six-month treatment period. After this period, there were no differences between the study groups in median ALT, AST, or bilirubin level at any laboratory visit or the number of patients with treatment-emergent liver enzyme elevation (380 mg XR-NTX 9%, 190 mg XR-NTX 12%; and placebo 15%). There was one case of hepatomegaly and one case of hepatitis C reported in each XR-NTX group, compared with no hepatic adverse events in the placebo group. Limitations of this study included its somewhat short duration and the exclusion of patients with coexisting severe psychiatric or substance use disorders and baseline AST or ALT greater than 3 times the upper limit of normal (>3× ULN).

A 2006 randomized controlled trial (n=1,383) sought to identify a cumulative benefit of various alcohol use disorder (AUD) treatments and reported adverse events related to hepatic safety.[2] The study excluded patients with liver enzyme levels >3× ULN and measured liver enzymes monthly during the 16-week treatment period with primary endpoint of percent days abstinent from alcohol and time to first heavy drinking day. Patients were treated with medication management using naltrexone (n=309), acamprosate (n=303), acamprosate, and naltrexone (n=305) with or without combined behavioral intervention (CBI) versus placebo (n=309). Patients received an average daily dose of 88 mg of naltrexone and 2,537 mg of acamprosate during the treatment period. Patients in all treatment groups reduced drinking. Twelve patients in the medication groups experienced treatment-emergent liver enzyme elevations >5× ULN (naltrexone 6, acamprosate 1, naltrexone+acamprosate 5) compared with zero in the placebo group ($P<.02$). All but two patients had normalization of their liver enzymes on follow-up. This study's generalizability was limited by excluding patients with coexisting psychiatric and substance use disorders.

A 2022 retrospective cohort study (n=160) followed liver enzymes in patients treated with oral or injectable naltrexone for AUD (100 had "liver disease" and, of those, 47 had cirrhosis) during a four-year period.[3] Liver disease was defined as the presence of radiographic abnormalities, such as steatosis, in addition to laboratory abnormality (such as elevate liver enzymes). Liver disease was further defined as cirrhosis if patient had a fibrosis-4 score ≥3.25; an International Classification of Diseases, Tenth Revision (ICD-10) code for cirrhosis; or radiographic evidence of liver nodularity or portal hypertension in addition to elevated INR or thrombocytopenia. The cohorts with liver disease and cirrhosis saw a decrease in mean liver enzymes during and after treatment (see **TABLE**). The

TABLE. Mean liver enzyme values in a cohort of 160 patients taking naltrexone (oral or injectable) for alcohol use disorder[3]

Value	Before (mean)	During (mean)	Before/During *P* value	After (mean)	Before/After *P* value
Liver disease group					
AST (IU/L)	59	46	0.001	36	<0.001
ALT(IU/L)	39	32	0.01	28	<0.001
Alkaline phosphatase (IU/L)	98	94	0.26	100	0.43
Total bilirubin (mg/dL)	0.86	0.82	0.54	0.56	0.003
Cirrhosis group					
AST (IU/L)	80	49	<0.001	47	<0.001
ALT (IU/L)	39	32	<0.001	28	<0.001
Alkaline phosphatase (IU/L)	108	100	0.12	101	0.52
Total bilirubin (mg/dL)	1.25	1.01	0.18	0.87	0.01

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

cohort without liver disease saw no changes in mean liver enzymes before/during/after treatment except for total serum bilirubin (0.4, 0.52, and 0.19 mg/dL, respectively; *P*=.02, *P*=.03). Limitations included the lack of a comparison group of patients not taking naltrexone.

A larger 2022 retrospective cohort study (n=9,635) analyzed 3,906 patients with AUD that underwent pharmacologic treatment, including 1,135 with alcohol-associated liver disease (ALD) for a mean follow-up period of 9.2 years.[4] Patients from a patient database were identified as having ALD or AUD based on the presence of predefined ICD-10 codes, such as alcoholic hepatitis, alcoholic cirrhosis, and alcohol dependence. The researchers assessed whether initiation of medications for AUD was associated with a decreased adjusted odds ratio (aOR) of developing ALD or progressing from ALD to a hepatic decompensation event (which was not clearly defined in this study). Compared with nonpharmacologic treatment, medications used for AUD were associated with a decreased incidence of ALD (aOR 0.37; 95% CI, 0.31–0.43; *P*<.001). The association was seen with naltrexone (aOR 0.67; 95% CI, 0.46–0.95; *P*=.03), gabapentin (aOR 0.36; 95% CI, 0.30–0.43; *P*<.001), topiramate (aOR 0.47; 95% CI, 0.32–0.66; *P*<.001), and baclofen (aOR 0.57; 95% CI, 0.36–0.88; *P*=.01). Furthermore, there were lower rates of hepatic decompensation in patients with cirrhosis who were treated with naltrexone (aOR 0.27; 95% CI, 0.10–0.64; *P*=.05) and gabapentin (aOR 0.36; 95% CI, 0.23–0.56; *P*<.001). Limitations of this study included the lack of a clear definition of hepatic decompensation, reliance upon ICD-10 codes that are difficult to assess for accuracy, and a relative homogenous patient demographic. EBP

André Biscaye, MD
William E. Michael, MD
Department of Family Medicine and Community Health, University of Wisconsin, Madison, WI

The corresponding author is William Michael; william.michael@fammed.wisc.edu.
The authors declare no conflicts of interest.

References

1. Lucey MR, Silverman BL, Illeperuma A, O'Brien CP. Hepatic safety of once-monthly injectable extended-release naltrexone administered to actively drinking alcoholics. *Alcohol Clin Exp Res.* 2008; 32(3):498–504. [STEP 3]
2. Anton R. Combined Pharmacotherapies and behavioral interventions for alcohol dependence: the Combine Study: a randomized controlled trial. *JAMA*. 2006; 295(17): 2003–2017. [STEP 3]
3. Ayyala D, Bottyan T, Tien C, et al. Naltrexone for alcohol use disorder: hepatic safety in patients with and without liver disease. *Hepatol Commun*. 2022; 6(12):3433–3442. [STEP 3]
4. Vannier AG, Shay JE, Fomin V, et al. Incidence and progression of alcohol-associated liver disease after medical therapy for alcohol use disorder. *JAMA Netw Open*. 2022; 5(5):e2213014. [STEP 3]

Do intra-articular corticosteroid injections help delay knee replacement surgery in patients with knee osteoarthritis?

EVIDENCE-BASED ANSWER

The evidence is conflicting. Corticosteroid injections (CSI) are not associated with a reduced risk total knee arthroplasty (TKA) in patients with knee osteoarthritis (strength of recommendation [SOR]: **B**, meta-analysis of 2 cohort studies). But CSI may increase time to TKA, although the clinical significance of this delay is unknown (SOR: **B**, based on 2 cohort studies).

DOI 10.1097/EBP.0000000000002046

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

A 2022 meta-analysis of 40 studies including randomized controlled trials, cohort studies, and case–control studies (N=6,041,254) examined the effect of medications, including corticosteroid injections (CSIs), on risk of total knee arthroplasty (TKA) or total hip arthroplasty (THA) in patients with osteoarthritis (OA).[1] Two of the included retrospective cohort studies evaluated the risk of knee arthroplasty and CSI. One retrospective cohort study compared matched 684 patients with mild-to-moderate knee radiographic OA who did or did not initiate CSI. Over 48 months, 33 (22%) in the CSI cohort versus 29 (5.4%) of the comparison cohort received TKAs. The second study followed 656 patients with OA, of which 143 (22%) received CSI. CSI did not increase the five-year risk of incident TKA. The 2022 meta-analysis authors concluded that CSI did not decrease the risk of TKA (risk ratio [RR] 2.0; 95% CI, 0.57–6.8) compared with nonusers. This meta-analysis was limited by high heterogeneity between the cohort studies (I^2=79%).

A 2021 retrospective cohort study used CPT codes to investigate time to TKA or THA after intra-articular injection in 3,340 patients at a single academic medical institution from January 2018 to December 2018.[2] Patients were excluded if they underwent a nonelective surgery (i.e., trauma or revision) or had less than two weeks of data in the medical record. The primary outcome was the time between the first presentation to an orthopedic clinic and a TKA or THA. Of the 1,570 patients who received a TKA, 192 received preoperative injections (12%) including 23 who received CSI alone and 28 who received both CSI and hyaluronic acid injections (HAIs). Of the patients who received CSI, 16 of 23 (70%) received just one injection. There were no significant differences between the treatment (injection) and control (no-injection) groups in age, BMI, race, gender, or medical complexity as assessed by the Charlson Comorbidity index. Time from first clinical presentation to TKA was greater in patients who received injections compared with those who did not (20 vs 11.6 months; $P<.001$). The TKA delay was similar between HAI and CSI (19.9 vs 14.1 months, $P=.10$). The study was limited by potential selection bias: patients who receive injections are likely to want surgical delay, injections delay surgery because of risk of infection, and the degree or severity of arthritis was unknown. Additionally, a variety of different CSI types were included, making it difficult to assess the efficacy of a single injection type or dose.

A 2022 retrospective analysis of a national claims database investigated time to TKA after CSI or HAI.[3] Patients who underwent an intra-articular knee injection on the same day as a diagnostic code for knee-related pain, effusion, or OA (n=141,574) were compared with patients with the same knee-related diagnostic codes without a history of intra-articular knee injection (n=637,112). Eligible patients were 50 to 70 years old at the time of their first injection or knee-related diagnosis. Patients were excluded if they received both CSI and HAI, if their chart lacked CPT modifiers related to injection laterality, or if they had a history of platelet-rich plasma injection in the knee. Outcome measures included average time to TKA from the date of knee-related diagnosis. There were significant differences in age, sex, race, and Elixhauser Comorbidity Index between the exposure (CSI and HAI) and control groups (no-injection). Of the 141,574 patients who received injections, 124,129 (87%) received CSI and 17,445 (13%) received HAI. Most of the CSI group received only one injection total (n=80,664, 65%). Average time to TKA was 342 days in the noninjection control group compared with 616 days for those who received one CSI (*P* value not included). The 10-year conversion to TKA incidence was highest in HAI cohort

at 32%, followed by the CSI cohort at 24%, and the non-injection cohort at 7.3% ($P<.001$).

A 2020 observational prospective cohort study evaluated the risk of total or partial knee arthroplasty in patients with or at risk of developing knee OA (n=4,796).[4] Patients were aged 45 to 79 years old with OA or at risk of developing knee OA. Researchers excluded patients with inflammatory arthritis and bilateral end-stage OA of the knee. Patients were followed annually for up to nine years, and after excluding patients lost to follow-up, 3,822 patients were included in the analysis with just over half being female (58%) and a mean baseline age of 61 years old. The authors used propensity score matching to match patients with available controls (n=1,366). The authors found that each CSI was associated with an increased risk of total or partial knee arthroplasty in patients with or at risk for OA (hazard ratio [HR] 1.6; 95% CI, 1.4–1.8). Limitations of the study included that a proportion of the patients who received CSI also received HAI; however, the authors attempt to account for this by controlling for HAI as a covariate (where HAI did not alter the analysis results). Additionally, although time-dependent propensity score matching was used, it was still possible to have residual confounding because of unmeasured variables. EBP

Rebecca Mullen, MD, MPH
Jennifer Kordell, MD
University of Colorado Family Medicine Residency, Aurora, CO

The Corresponding Faculty Author on the manuscript is Rebecca Mullen, MD, MPH; Rebecca.mullen@cuanschutz.edu
The authors declare no conflicts of interest.

References

1. Cui B, Chen Y, Tian Y, et al. Effects of medications on incidence and risk of knee and hip joint replacement in patients with osteoarthritis: a systematic review and meta-analysis. *Adv Rheumatol*. 2022; 62(22):1–11. [STEP 1]
2. Tang A, Almetwali O, Zak SG, Bernstein JA, Schwarzkopf R, Aggarwal VK. Do preoperative intra-articular corticosteroid and hyaluronic acid injections affect time to total joint arthroplasty? *J Clin Orthop Trauma*. 2021; 16:49–57. Erratum in: J Clin Orthop Trauma. 2021; 21:101558. [STEP 3]
3. Pirkle S, Seidel H, Bhattacharjee S, Shi LL, Lee MJ, Strelzow JA. Analysis of the cost and efficacy of intra-articular knee injections. *J Am Acad Orthop Surg Glob Res Rev*. 2022; 6(2): e2100203. [STEP 3]
4. Wijn SRW, Rovers MM, van Tienen TG, Hannink G. Intra-articular corticosteroid injections increase the risk of requiring knee arthroplasty. *Bone Joint J*. 2020; 102-B(5):586–592. [STEP 3]

Is CBT effective for treating delayed sleep onset in adults?

EVIDENCE-BASED ANSWER

Yes. Cognitive behavioral therapy is effective for treating delayed sleep onset in adults, including those with comorbidities, reducing time to sleep onset by 19 to 22 minutes (SOR: **B**, 1 meta-analysis of randomized controlled trials [RCTs], 2 additional RCTs, 1 longitudinal cohort).

DOI 10.1097/EBP.0000000000002031

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

A 2015 systematic review and meta-analysis of 20 randomized controlled trials (RCTs) described the effect of cognitive behavioral therapy (CBT) versus inactive comparators for treatment of chronic insomnia in adults (N=1,162).[1] The review included adults diagnosed with chronic insomnia who did not have medical, psychiatric, or other sleep disorders. Patients received three or more modalities (cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation) delivered on at least two occasions. Sixteen trials evaluated sleep onset latency (SOL) within four weeks posttreatment, showing a reduction in SOL in the CBT group compared with inactive comparators (16 trials; N not provided; mean difference 19 minutes; 95% CI, –14 to –24; I^2=42%). The study was of moderate quality, limited by lack of blinded comparisons.

A 2019 RCT evaluated the effectiveness of CBT in adults with chronic insomnia and fibromyalgia at baseline, posttreatment, and at six months (n=113).[2] Patients were randomly assigned to three groups: eight individual training sessions of CBT for insomnia (n=39), eight individual sessions of CBT for pain (n=37), or waitlist control (n=37). Patients receiving CBT for insomnia showed improvement in SOL from 58 minutes baseline to 22 minutes posttreatment (effect size [ES]=1.1) and 34 minutes at six months (ES=0.7; comparison statistic not provided; ES is the magnitude of improvement from baseline, interpreted as 0.2=small, 0.5=medium, and

0.8=large). The study was of moderate quality because of lack of blinded comparison, small sample size, and potential confounding by comorbid chronic pain.

A 2018 two-arm, parallel group RCT compared CBT with sleep hygiene education (SHE) delivered online to 1,711 patients with insomnia, including those with comorbidities.[3] The primary outcomes of the study included sleep-related quality of life measured by the sleep condition indicator (SCI) assessed at 0, 4, 8, and 24 weeks. The SCI is an 8-item survey of 0 to 32 points, including a question on difficulty falling asleep, with higher scores indicating better sleep. The study showed greater improvement in SCI scores of the CBT group compared with the SHE group at four weeks (adjusted mean differences [aMD] 2.9 points; 95% CI, 2.3–3.5), at eight weeks (aMD 4.9; 95% CI, 4.3–5.5), and at 24 weeks (aMD 4.9; 95% CI, 4.3–5.6). The study was of moderate quality because of lack of blinded comparison and inclusion of participants with comorbidities.

A 2021 longitudinal study evaluated one- and 10-year outcomes of an RCT of CBT for the treatment of insomnia (n=133).[4] Patients received an insomnia-specific CBT self-help workbook and six weeks of therapist guidance or no guidance. They were evaluated posttreatment and one year, and 10 years posttreatment using the insomnia severity index. The insomnia severity index is a 7-item survey that includes assessment of difficulty falling asleep, scored from 0 to 28, with higher scores indicating greater severity. At baseline, the mean insomnia severity index score (M) of all patients was 18.3. Patients receiving guidance had better scores posttreatment (M 7.6) and at one year (M 7.9). Unguided participants also had better scores posttreatment (M 11.5) and at one year (M 9.8). The difference between guided and unguided treatment response was significant immediately after therapy (difference 3.9; P=.003) but not at one or 10 years. The review was of moderate quality because of lack of an untreated control group at follow-up and small sample size. EBP

Nadine Nixon, MD
Whitney Keiffer-Sharp, DO
Courtney Lynn, DO
Nicole Schmitz, DO
Prevea Family Medicine Residency Program, Eau Claire, WI

The corresponding author is Nadine Nixon, MD; nnixonmd@gmail.com
The authors declare no conflicts of interest.

References

1. Trauer JM, Qian MY, Doyle JS, et al. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. *Ann Intern Med*. 2015; 163(3):191–204. [STEP 1]
2. McCrae CS, Williams J, Roditi D, et al. Cognitive behavioral treatments for insomnia and pain in adults with comorbid chronic insomnia and fibromyalgia: clinical outcomes from the SPIN randomized controlled trial. *Sleep*. 2019; 42(3): zsy234. [STEP 2]
3. Espie CA, Emsley R, Kyle SD, et al. Effect of digital cognitive behavioral therapy for insomnia on health, psychological well-being, and sleep-related quality of life: a randomized clinical trial. *JAMA Psychiatry*. 2019; 76(1): 21–30. [STEP 2]
4. Jernelöv S, Blom K, Hentati Isacsson N, et al. Very long-term outcome of cognitive behavioral therapy for insomnia: one- and ten-year follow-up of a randomized controlled trial. *Cogn Behav Ther*. 2022; 51(1):72–88. [STEP 3]

Does CPAP adherence decrease mortality in those with OSA?

EVIDENCE-BASED ANSWER

No clearly demonstrated mortality benefit was noted from continuous positive airway pressure (CPAP) therapy in patients with obstructive sleep apnea (OSA; SOR: **B**, meta-analysis of limited quality randomized controlled trials). However, observational data suggest that CPAP treatment may be associated with reduced all-cause mortality in older men with OSA, with a number needed to treat as low as 10 to prevent one death at 11 years of follow-up (SOR: **B**, large cohort study). Furthermore, early termination of CPAP therapy in patients with OSA is associated with increased mortality, with a number needed to harm of 72 at three years (SOR: **B**, large cohort study).

DOI 10.1097/EBP.0000000000002033

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

A 2016 meta-analysis (18 randomized controlled trials [RCTs]; N=4,146) investigated the effect of

continuous positive airway pressure (CPAP) therapy on all-cause mortality in patients with obstructive sleep apnea (OSA).[1] Patients consisted of adults (18–85 years old; 75% male) with OSA, with most studies defining this as an apnea–hypoxia index of 10 or more. The studied intervention was treatment with CPAP at night, with mean treatment duration of five hours. Controls included no treatment, sham CPAP (wear of a CPAP apparatus delivering subtherapeutic pressure), or nocturnal supplemental oxygen. All-cause mortality was one of the outcomes of interest, with patients followed for six months to five years. CPAP treatment in OSA patients did not result in a significant decrease in all-cause mortality when compared with controls (4 RCTs, N=2,020; odds ratio [OR] 0.85; 95% CI, 0.35–2.1). Studies were limited by short follow-up length and small study size, resulting in decreased power to detect a mortality benefit, as well as poorly defined and variable adherence to CPAP therapy.

A 2015 retrospective cohort study (n=25,389) evaluated the association between OSA and all-cause mortality in adults with or without CPAP treatment.[2] Patients were adults 20 years old and older who received an *International Classification of Diseases*-10 coded diagnosis of OSA between 1999 and 2009 in the Danish National Patient Registry. Researchers divided patients into two cohorts: those treated with CPAP therapy within the first two years of diagnosis and those not treated. The authors did not further delineate the specifics of the treatment. The primary outcome was all-cause mortality with up to 11 years of follow-up. The researchers did additional subgroup analysis, dividing the cohorts by age and gender. Overall, CPAP treatment in adults with OSA was not associated with decreased all-cause mortality compared with no CPAP treatment (hazard ratio [HR] 0.72; 95% CI, 0.39–1.3). However, in the subgroup of patients 40 to 59 years old, CPAP was associated with improved survival, with a number needed to treat (NNT) of 52 to prevent one death at 11 years (HR 0.67; 95% CI, 0.56–0.79). The survival benefit from CPAP was even larger in patients >60 years old, with an NNT of 10 to prevent one death at 11 years (HR 0.62; 95% CI, 0.54–0.71). When looking only at women with OSA, CPAP treatment was not associated with a significant difference in all-cause mortality. Limitations included differences in indications to start CPAP in the United States versus Denmark and uncertain treatment compliance.

A 2022 cohort study (n=176,014) looked at the potential effect of CPAP termination on all-cause mortality in patients with OSA.[3] Researchers included adults (mean age 60 years old, 36% women) with a diagnosis of OSA and new treatment with CPAP, identified by diagnosis and treatment codes in the French national health insurance reimbursement database. Researchers identified a cohort of patients who stopped CPAP within the first year of therapy and used propensity score matching to form a comparator cohort who continued treatment for at least one year. CPAP termination was assumed to be linked with nonadherence and those with a valid and documented reason for stopping CPAP were censored from analysis. The primary outcome was all-cause mortality with a follow-up period of three years after CPAP termination. Terminating CPAP treatment within the first year was associated with an increased risk of all-cause mortality compared with those who continued treatment, with a number needed to harm of 72 to cause one death at three years of follow-up (HR 0.61; 95% CI, 0.57–0.65). Limitations included unavailable data on OSA severity, adherence to CPAP, and OSA symptoms. EBP

Gavin Yseth, DO
Joel Herness, MD
David Grant Medical Center Family Medicine Residency, Travis AFB, CA

The corresponding author is Joel Herness, MD; joelherness@gmail.com

The authors declare no conflicts of interest.

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

References

1. Guo J, Sun Y, Xue LJ, et al. Effect of CPAP therapy on cardiovascular events and mortality in patients with obstructive sleep apnea: a meta-analysis. *Sleep Breath*. 2016; 20(3):965–974. [STEP 1]
2. Jennum P, Tønnesen P, Ibsen R, Kjellberg J. All-cause mortality from obstructive sleep apnea in male and female patients with and without continuous positive airway pressure treatment: a registry study with 10 years of follow-up. *Sleep Med*. 2015; 16. [STEP 2]
3. Pépin JL, Bailly S, Rinder P, et al. Relationship between CPAP termination and all-cause mortality: a French nationwide database analysis. *Chest*. 2022; 161(6):1657–1665. [STEP 2]

Does the use of procalcitonin and C-reactive protein to guide antibiotic use decrease antibiotic duration in hospitalized patients?

EVIDENCE-BASED ANSWER

In hospitalized patients with sepsis or respiratory tract infections, procalcitonin-guided therapy significantly reduces the duration of antibiotic usage (SOR: **A**, systematic review and meta-analyses of randomized controlled trials [RCTs]). C-reactive protein–guided therapy may reduce antibiotic duration by one or two days compared with placebo (SOR: **C**, conflicting RCTs).

DOI 10.1097/EBP.0000000000002050

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

A 2022 systematic review and meta-analysis of 27 randomized controlled trials examined the duration of antibiotic use in hospitalized adults using biomarker guidance versus usual care or standard guidelines (25 studies of procalcitonin [PCT] and 2 studies of C-reactive protein [CRP]; N=7,521).[1] About half of the included patients (N=3,665, 50.5%) were in an intensive care unit (ICU) compared with a general ward (N=3,586, 49.5%). Most patients were diagnosed with sepsis or respiratory tract infections. Antibiotics were decreased or discontinued according to PCT or CRP levels in the intervention groups, whereas control groups received standard care or followed current antibiotic guidelines. Standard treatment typically included 7 to 10 days of antibiotics. The primary outcome was duration of antibiotic therapy, with secondary outcomes including length of hospitalization, in-hospital and 28-day mortality, and infection recurrence. PCT-guided therapy resulted in a moderate reduction in the duration of antibiotic therapy (standard mean difference [SMD] –0.59; 95% CI, –0.85 to –0.33). The primary outcome was inconsistent in the subset of two CRP-guided studies; one study (n=503) found no statistically significant difference in duration, whereas the other study (n=7,018) found a reduced median interquartile range of antibiotic durations (5–8 days in the CRP group vs 7–11 days in the control group; $P=.011$). Most studies had high risk of bias, largely because of incomplete blinding and poor protocol adherence; most studies reported intention-to-treat data only. High heterogeneity was noted among the results of the PCT-guided studies.

The systematic review also identified a 2013 multicenter randomized open clinical trial (n=94) that examined the effectiveness of PCT compared with CRP in guiding antibiotic therapy in adult ICU patients with sepsis or septic shock.[2] The mean age was 60 years old. Patients who were anticipated to require long-term antibiotic therapy or who had more than 48 hours of antibiotic therapy before screening were excluded. The primary outcome was duration of antibiotic therapy for the first episode of infection. Additional measures included the overall duration of antibiotic treatment, duration without antibiotic treatment, mortality rate from any cause within 28 days of hospitalization, ICU and hospital length of stay, as well as clinical recovery, relapse, and hospital-acquired infection. No difference was noted between groups in median duration of antibiotic therapy for the first episode of infection or overall antibiotic exposure. EBP

Amanda Allmon, MD
Brittney Marshall, MD
Magdaleno Gutierrez, MD
Angela Ash, MD
University of Missouri-Columbia, Columbia, MO

The corresponding author is Amanda Allmon; allmona@health.missouri.edu.
The authors declare no conflicts of interest.

References

1. Elnajdy D, El-Dahiyat F. Antibiotics duration guided by biomarkers in hospitalized adult patients; a systematic review and meta-analysis. *Infect Dis*. 2022; 54(6):387–402. [STEP 1]
2. Oliveira CF, Botoni FA, Oliveira CR, et al. Procalcitonin versus C-reactive protein for guiding antibiotic therapy in sepsis: a randomized trial. *Crit Care Med*. 2013; 41(10):2336–2343. [STEP 2]

What is the net cost/benefit for extent of in-office discussion, measured in financial terms and patient satisfaction ratings?

EVIDENCE-BASED ANSWER

In-office patient–clinician communication is significantly associated with less emergency room or hospital utilization (SOR: **B**, systematic review of cross-sectional, cohort, and case–control studies, and 1 cohort study) and less annual patient spending on healthcare (SOR: **C**, 1 cohort study). A higher number of weekly clinic hours is significantly associated with higher patient satisfaction (SOR: **C**, 1 cross-sectional study).

DOI 10.1097/EBP.0000000000002102

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

A 2021 systematic review of 19 studies (N=388,280), consisting of cross-sectional, cohort, and case–control studies, evaluated associations between the consumer assessment of healthcare providers and systems (CAHPS) composite ratings, including in-office patient–clinician communication (PCC), and clinical outcomes.[1] Of the 19 studies, three studies (N=251,632) addressed PCC. Patient demographics varied by study, with age ranging from 30 to 75 years old; no other specific demographic information was provided. Patients were included if they had hepatic, pancreatic, or biliary disease; atherosclerotic cardiovascular disease (ASCVD); or were Medicare beneficiaries with a personal doctor. Outcomes included patient experiences with healthcare utilization (emergency room [ER] visits, hospitalizations, healthcare expenditures, and global rating of the physician by patients). Global rating of the physician was reported on a 0 to 100 scale, with higher scores indicating more favorable rating. PPC was a composite variable calculated from four CAHPS questions answered on a 4-point Likert scale (1 = never, 2 = sometimes, 3 = usually, and 4 = always), with a higher score indicating a higher level of PPC. The four questions dealt with whether clinicians spent enough time with you, gave understandable explanations, showed respect, and listened carefully. Poor PPC was associated with two or more ER visits per year (2 studies; N=8,761) but not with two or more hospitalizations per year. Favorable PPC was associated with a higher global rating of the physician (1 study; n=242,871; $P<.05$). The associations between PPC and overall healthcare expenditures and out-of-pocket expenses were inconsistent. Hepatopancreatobiliary patients who identified poor PPC did not spend more on overall healthcare expenditures (1 study; n=1,951); however, adult patients with ASCVD who identified poor PPC spent significantly more on healthcare annually (mean difference [MD] $1,243; 95% CI, $127–$2,359; $P<.05$). The systematic review was limited by low response rates in some studies and limited generalizability.

A 2019 retrospective cohort study (n=47,969), which was not included in the systematic review study above, compared PCC with ER visits, hospitalizations, and annual healthcare costs.[2] Patients were noninstitutionalized adults 18 years old or older (mean age 51.4 years old), with 58% female. The data were obtained from the 2010 to 2013 MEPS (medical expenditure panel survey), of which CAHPS was a component. Information regarding healthcare expenditures was obtained from MEPS data, based on direct out-of-pocket and insurance payments. PCC was calculated by dividing the sum of patient responses (range, 4–12) by the number of questions (4) to yield a composite variable on a scale of 1 (poor) to 3 (optimal). Compared with patients who rated their clinicians as "poor" communicators, patients who reported "optimal" communication had significantly lower odds of more than one ER visit (odds ratio [OR] 0.69; 95% CI, 0.53–0.91), more than one hospitalization (OR 0.67; 95% CI, 0.47–0.95), and they spent significantly less on annual healthcare (mean difference [MD] $1,865; 95% CI, $864–$2,865; $P<.05$). This study was limited by possible recall bias and inability to determine causality.

A 2018 cross-sectional study (n=1,540) used Swiss data from the QUALICOPC (quality and costs of primary care) survey to examine the association between patient satisfaction with physician communication.[3] This study was not included in the systematic review above. Patients

were 56% female with a median age of 59 years old, and 52% rated their perceived health as "good." Outcomes included practice level information such as number of daily face-to-face consultations and number of weekly patient contact hours. Patient satisfaction with physician communication was calculated as a sum of patient responses to 15 questions, with negative answers coded as 0, and positive answers coded as 1, giving a range of 0–15 points. Higher scores indicated better satisfaction. Patient satisfaction with physician communication was significantly lower when physicians reported a higher number of daily face-to-face consultations (incidence rate ratio [IRR] 1.16; 95% CI, 1.08–1.25). However, patients were significantly less likely to report poor communication when their physician reported a higher number of weekly patient contact hours (IRR 0.87; 95% CI, 0.81–0.93). EBP

John Petrilli, MD, FAAFP
University of South Florida Morsani College of Medicine, Department of Family Medicine, Tampa, FL

The corresponding author is John Petrilli; jpe@usf.edu.
The authors declare no conflicts of interest.

References

1. Navarro S, Ochoa CY, Chan E, Du S, Farias AJ. Will improvements in patient experience with care impact clinical and quality of care outcomes?: a systematic review. *Med Care*. 2021; 59(9):843–856. [STEP 2]
2. Nasir K, Okunrintemi V. Association of patient-reported experiences with health resource utilization and cost among US adult population, medical expenditure panel survey (MEPS), 2010-13. *Int J Qual Health Care*. 2019; 31(7): 547–555. [STEP 3]
3. Cohidon C, Wild P, Senn N. Patient experience in primary care: association with patient, physician and practice characteristics in a fee-for-service system. *Swiss Med Wkly*. 2018; 148:w14601. [STEP 3]

Does food insecurity increase the risk of metabolic syndrome or obesity?

EVIDENCE-BASED ANSWER

Food insecurity increases the risk for obesity in all patients (SOR: B, meta-analysis of mixed study types). Adult patients with low food security are at an increased risk of metabolic syndrome compared with those with higher food security (SOR: B, cohort studies). For adolescents, there is no association between food security and metabolic syndrome (SOR B, cohort study).

DOI 10.1097/EBP.0000000000002090

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

A 2022 mixed-method systematic review and meta-analysis of 36 quantitative studies (cross-sectional, cohort, and case–control studies) and 11 qualitative studies assessed the effect of food insecurity on body mass index (BMI). Researchers defined food insecurity as limited or uncertain availability of nutritionally adequate and safe foods or limited or uncertain ability to acquire acceptable foods in socially acceptable ways. The studies included children and adults in high-income countries but excluded those with BMI of >40kg/m^2. Twenty-four of the quantitative studies (N=36,113) were reviewed and collectively showed a statistically significant association between food insecurity and obesity (odds ratio [OR] 1.5; 95% CI, 1.4–1.6). Analysis of the qualitative studies supported these findings, identifying that due to their accessibility and affordability, participants with food insecurity relied more on energy dense but nutrient poor foods, which may have contributed to obesity rates. Limitations of this study included differing assessment tools for food insecurity in each study and lack of longitudinal data.[1]

A 2020 cohort study from the U.S. National Health and Nutrition Examination Surveys (NHANES) from 2007 to 2014 addressed the association between food insecurity and the risk of metabolic syndrome (MetS) in adult women (n=4,249). Food insecurity was defined as limited or uncertain availability of safe and nutritionally adequate foods or limited or uncertain ability to acquire food in socially acceptable ways and was measured using the Household Food Security Scale questionnaire. Participants had an examination that included the components of MetS (including at least 3 of 5 of the following criteria: waist circumference ≥88 cm in women, triglycerides >150 mg/mL, HDL<50 mg/dL, blood pressure ≥130/85 mmHg, and fasting glucose>100 mg/

dL). Of the sample, 77% reported being food secure, 9% had marginal, 8% had low, and 6% had very low food security. After adjusting for sociodemographic factors, women were found to have an increased risk of MetS if they had low (OR 1.4; 95% CI 1.1–1.8) or very low (OR 1.7; 95% CI, 1.3–2.2) food security. Limitations of this study included using self-reported data and data measured only at the household, not the individual, level.[2]

A 2010 cohort study from the U.S. National Health and Nutrition Examination Survey (NHANES) from 1999 to 2006 explored the impact of food insecurity on the risk of metabolic syndrome (MetS). The review included adolescents 12 to 19 years old (N=3,113) and adults older than 20 years (N=6,138). The study excluded pregnant women and those missing data required to determine food security or diagnose MetS. MetS was defined as having any three of five criteria: elevated waist circumference (≥102 cm in men, >88 cm in women); triglycerides ≥150 mg/mL; HDL cholesterol <40 mg/dL in men or <50 mg/dL in women; blood pressure >130/85 mmHg; or glucose>110 mg/dL (including diabetes). In adolescents, MetS was defined using the published age- and sex-specific criteria. Food insecurity was defined as not having enough food for an active healthy life due to the lack of resources. Using the Household Security Scale, 76% of participants were fully food secure, 8% had marginal, 11% had low, and 5% had very low food security. For adults, there was no significant difference in the odds of having metabolic syndrome across categories of household food security. However, when adjusting for race/ethnicity, sex, age, income, education, and smoking status, adults with marginal and very low food security were significantly more likely to have MetS (OR 1.8; 95% CI, 1.3–2.5 and OR 1.7; 95% CI, 1.1–2.4, respectively). In adolescents, there was no significant association between household food security and metabolic syndrome. The cross-sectional nature of the NHANES study does not allow a determine whether household food insecurity preceded metabolic syndrome.[3] EBP

Rebecca Lambert, MD[1,2]
Camdin Gray, MD[1,2]
Tara Kennedy, MD[1,2]
Katinka Hooyer, PhD[1,2]
[1]Froedtert & the Medical College of Wisconsin Menomonee Falls Residency Program, Menomonee Falls, WI
[2]Center for Healthy Communities and Research, Department of Family and Community Medicine, Medical College of Wisconsin, Milwaukee, WI

The corresponding author is Rebecca Lambert; relambert@mcw.edu.

The authors declare no conflicts of interest.

References

1. Eskandari F, Lake AA, Rose K, Butler M, O'Malley C. A mixed-method systematic review and meta-analysis of the influences of food environments and food insecurity on obesity in high-income countries. *Food Sci Nutr*. 2022; 10(11):3689-3723. [STEP 1]
2. Park S-H, Strauss SM. Food insecurity as a predictor of metabolic syndrome in U.S. female adults. *Public Health Nurs.* 2020;37(5):663-670. [STEP 3]
3. Parker ED, Widome R, Nettleton JA, Pereira MA. Food security and metabolic syndrome in U.S. Adults and adolescents: findings from the National Health and Nutrition Examination Survey, 1999–2006. *Ann Epidemiol*. 2010;20(5):364–370. [STEP 3]

Does testosterone supplementation improve sexual function in postmenopausal women?

EVIDENCE-BASED ANSWER

Testosterone supplementation (300 mcg per day transdermal or equivalent doses by other routes) leads to small improvements in several measures of sexual function in postmenopausal women, including slightly less than one more satisfying sexual event per month, with no serious short-term adverse effects (SOR: **A**, meta-analysis of randomized controlled trials). A trial of nonoral testosterone (eg, transdermal) can be considered in postmenopausal women with sexual dysfunction after performing a biopsychosocial evaluation and with routine monitoring of testosterone levels and clinical response (SOR: **C**, evidence-based guideline).

DOI 10.1097/EBP.0000000000002056

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

A 2019 systematic review and meta-analysis of 36 randomized controlled trials (RCTs; N=8,480) evaluated the efficacy and safety of systemic testosterone treatment for women, with 33 of the RCTs including only postmenopausal women (both natural and surgical).[1] The included trials were single and double-blind studies of at least 12-week duration that compared testosterone with placebo or a comparator arm (including estrogen with or without progesterone) in women 18 to 75 years old, with or without baseline sexual dysfunction (specific diagnostic criteria not reported). Most trials excluded women with dyspareunia, depression, or antidepressant use. Testosterone doses ranged from 50 to 300 mcg daily and were most often administered orally (15 trials) or by transdermal patch (13 trials). The reviewers only included outcome data from studies using the 300 mcg daily transdermal patch or equivalent dose for other forms in their pooled data analysis because this dose most often achieves a serum-free testosterone in the upper end of the premenopausal range. The studies ran from 12 weeks to two years and used a variety of validated self-administered outcome questionnaires, the number of satisfying sexual events over four weeks, and number of concerns regarding sexual function. Desire, arousal, orgasm, and responsiveness were assessed with different scales across the trials, so pooled results were reported as standardized mean differences. Postmenopausal women receiving testosterone supplementation compared with placebo or comparator had a small but significant increase in satisfying sexual events per month (8 trials, N=3,238; mean difference [MD] 0.85; 95% CI, 0.52–1.2; I^2=58%) and a small improvement in sexual desire score (15 trials, N=3,762; standardized mean difference [SMD] 0.36; 95% CI, 0.22–0.50; I^2=72%). Testosterone also led to small improvements in arousal (11 trials, N=3,271; SMD 0.28; 95% CI, 0.21–0.35; I^2=0.0%), orgasm (11 trials, N=3,289; SMD 0.25; 95% CI, 0.18–0.32; I^2=0.0%), pleasure (7 trials, N=3,006; MD 6.9; 95% CI, 5.2–8.5; I^2=0.0%), and responsiveness (8 trials, N=3,212; SMD 0.28; 95% CI, 0.21–0.35). Although oral testosterone resulted in a slight increase of LDL cholesterol compared with placebo or comparator (9 trials, N=637; mean difference 0.29 mmol/L; 95% CI, 0.04–0.53), no significant changes were seen when nonoral forms (transdermal patch, cream, or injectable) were used (10 trials, N=1,768; mean difference 0.02 mmol/L; 95% CI, –0.04 to 0.07). No serious adverse events (ie, acute myocardial infarction, stroke, deep vein thrombosis, or cardiovascular deaths) were noted with testosterone, although a small increased risk of weight gain, acne, and hair growth was reported. This systemic review was limited by the significant heterogeneity in some of the outcomes, several undefined outcome measures, and attrition bias in the randomly allocated placebo groups. In addition, no consistent diagnostic criteria for sexual dysfunction were present among studies, and several studies did not require sexual dysfunction as inclusion criteria.

In 2019, several international women's health and endocrinologic organizations released a global consensus position statement on the use of testosterone therapy for women that was developed by leaders of the organizations.[2] The evidence-based statement was based on the 2019 systematic review above and a 2017 meta-analysis, which consisted of seven RCTs included in the 2019 review. The position statement endorsed the use of systemic testosterone in postmenopausal women who have been diagnosed with hypoactive sexual desire disorder after completing a formal biopsychosocial assessment (Level of Evidence 1; based on systematic review of high-quality RCTs). The statement recommended against the use of oral testosterone because of negative impact on LDL levels (Level of Evidence 1) and recommended a trial of non-oral forms at dosages that result in approximate premenopausal physiological testosterone levels. The statement further held that a baseline total testosterone level should be measured before initiating treatment and repeated after three to six weeks (Level 2A; based on a nonrandomized study), that clinical response should be assessed every six months (expert opinion), and that supplementation should be discontinued if no clinical benefit is seen (Level of Evidence 1B; based on RCT). EBP

Nicholas Cook-Rostie, MD
Amy Olmschenk, MD
University of Minnesota Saint Cloud Family Medicine Residency program, St. Cloud, Minnesota

The corresponding author is Amy Olmschenk; amy.olmschenk@centracare.com

The authors declare no conflicts of interest.

References

1. Islam RM, Bell RJ, Green S, Page MJ, Davis SR. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. *Lancet Diabetes Endocrinol*. 2019;7(10):754-766. [STEP 1]
2. Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. *J Clin Endocrinol Metab*. 2019;104(10):4660-4666. [STEP 5]

Is osteopathic manipulative treatment effective for pain relief in plantar fasciitis?

EVIDENCE-BASED ANSWER

Evidence is scant. Manual therapy in combination with a self-stretching protocol may improve physical function scores and marginally improve pain scores after four weeks of treatment when compared with a self-stretching protocol alone (SOR: **C**, small randomized controlled trial). Manual therapy also may improve short-term posttreatment symptoms in patients with plantar fasciitis compared with those taking a placebo medication (SOR: **C**, low-quality cross-over trial).

DOI 10.1097/EBP.0000000000002049

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

A 2011 single-blinded randomized controlled trial (n=60) investigated the effect of myofascial trigger point manual therapy on the treatment of plantar fasciitis pain.[1] Patients were 18 to 60 years old (mean age 44 years old; 75% female) with a clinical diagnosis of plantar heel pain. Patients came from a single physical therapy clinic in Brazil. The treatment group received weekly manipulation therapy in addition to completing a self-stretching protocol, whereas a control group received only the self-stretching protocol. The self-stretching protocol was performed twice daily for the entirety of the four-week study. Patients were excluded if they had contraindications to manual therapy, any prior manual therapy to their lower extremities, prior surgery on the effected extremity, or a fibromyalgia diagnosis. The outcomes of the study included changes in patient response to items from the SF-36 questionnaire (physical function and bodily pain sores range from 0 to 100, with 100 indicating improved function and worsening pain, respectively, with a minimal clinically important difference of 7.8 points between groups) at the time of presentation versus the end of the treatment protocol. The treatment group had improvements in both physical function scores (mean difference [MD] 9.3; 95% CI, 3.9–15) and bodily pain scores (MD 7.8; 95% CI, 2.5–13) compared with the control group. This study was limited by a lack of tracking patient compliance with the self-stretching protocol.

A 2006 single-blinded, randomized crossover (n=20) trial compared the effect of counterstrain osteopathic manipulative treatment (OMT) with placebo tablets.[2] Twenty patients (80% women; 20–66 years old) participated in the study, and all were clinically diagnosed with plantar fasciitis. Patients were excluded if they were obese, taking muscle relaxants, pain medication, or more than half the daily maximum dose of NSAIDs. The treatment group received counterstrain weekly for three weeks (of phase 1), whereas the control group received placebo capsules taken twice daily. After a two- to four-week washout period, the group interventions were reversed. Patients filled out symptom severity questionnaires at each of the three laboratory visits with ratings of five factors including pain, soreness, stiffness, mobility, and effect on sleep on a scale of zero (no symptoms) to nine (extreme symptoms/pain), with the sum being averaged. Symptom severity decreased directly after treatment with counterstrain in all three laboratory visits of the counterstrain phase and only the first visit in the control group (**TABLE**). No significant difference was noted between the counterstrain and control groups after six days of posttreatment. This study was limited by grouping pain with other symptoms in a composite severity score and by a lack of statistical comparison of changes between groups. EBP

TABLE. Mean symptom severity rating[a] per visit in a randomized crossover study (n=20) evaluating counterstrain OMT versus oral placebo pill for plantar fasciitis[2]

	Pretreatment	Posttreatment
Counterstain phase		
Visit 1	12	4[b]
Visit 2	8	4[b]
Visit 3	8	5[b]
Control phase		
Visit 1	10	8[b]
Visit 2	8	7
Visit 3	8	7

[a] Pain, soreness, stiffness, mobility, and effect on sleep; all measured on a 0- to 9-point scale (range 0–45). [b] *P*-value <.05 between pretherapy and posttherapy.

Jacquelynn Hatch, DO
Kimberly Berke, MD
Andrew Chambers, DO
Trinity Health Livingston Family Medicine Residency, Howell, MI

The corresponding author is Jacquelynn Hatch, DO; Jacquelynn_Hatch@ihacares.com
The authors have no conflicts of interest to declare.

References

1. Renan-Ordine R, Alburquerque-Sendín F, de Souza DP, et al. Effectiveness of myofascial trigger point manual therapy combined with a self-stretching protocol for the management of plantar heel pain: a randomized controlled trial. *J Orthop Sports Phys Ther*. 2011;41(2):43-50. [STEP 2]
2. Wynne MM, Burns JM, Eland DC, et al. Effect of counterstrain on stretch reflexes, hoffmann reflexes, and clinical outcomes in subjects with plantar fasciitis. *J Am Osteopath Assoc*. 2006;106(9):547-556. Erratum in: J Am Osteopath Assoc. 2006;106(11):636. [STEP 2]

Is cognitive behavioral therapy an effective treatment approach for adult ADHD?

EVIDENCE-BASED ANSWER

Cognitive behavioral therapy (CBT) is effective in the treatment of adult ADHD (SOR: **B**, 2 small randomized controlled trials [RCTs]). CBT with medication is significantly more likely to improve inattention symptoms and quality of life than medication only (SOR: **C**, small RCT). CBT with treatment as usual (TAU) is significantly more likely to be effective for ADHD core symptoms than TAU only (SOR: **C**, small RCT).

DOI 10.1097/EBP.0000000000002051

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

A 2021 multidimensional randomized controlled trial (RCT; n=98) examined the effectiveness of cognitive behavioral therapy (CBT) for adult ADHD.[1] Patients were diagnosed with ADHD, and 59% were male. Their age ranged from 18 to 45 years old with a mean age of 25.8 years old. Patients were included if they were stable with their current medication such as Concerta and Strattera, with <10% dosage fluctuations for at least one month. Patients with a current severe mental disorder, suicide risk, IQ <80, or unstable physical conditions were excluded. Patients were randomly assigned to a medication only group (M; dosage information not provided; n=49) or a medication with CBT group (CBT+M; n=49). CBT consisted of 12 weekly sessions lasting 120 minutes. Both groups were evaluated at baseline (T1), 12 weeks (T2), 36 weeks (T3), and 42 weeks (T4). The primary outcome was ADHD core symptoms that were measured by a self-reported ADHD rating scale (ADHD-RS; range 0–54) and Connors' adult ADHD rating scale—self-report screening version (CAARS; range 0–78), with higher scores reflecting more severe symptoms for both scales. CAARS consisted of items measuring the severity of difficulty in the time management and organization function that constituted the focus of CBT. Secondary outcomes included anxiety, depression, automatic thoughts, and quality of life. Anxiety and depression were measured using emotional symptoms through Self-rating Anxiety Scale (SAS; range 20–80) and Self-rating Depression Scale (SDS; range 20–80), with higher scores indicating more severe symptoms for both scales. Negative automatic thoughts were measured using Automatic Thoughts Questionnaire (ATQ; range 30–150), with higher scores indicating higher frequency of negative thoughts. Quality of life was measured using the World Health Organization Quality of Life—Brief Version (WHOQOL-BREF), with higher scores indicating higher quality (range 0–100). State-Trait Anxiety Inventory (STAI) evaluates state and trait anxiety (range 20–80, higher scores indicating worse anxiety). Compared with the M group, the CBT+M group had significantly lower ADHD core symptoms and anxiety and depression, but higher quality of life at subsequent time points (**TABLE**). No harms were noted in either group. This study was limited by high IQ, small sample size, and year of education of patients not representative of the population.

A 2017 RCT (n=60) compared the effectiveness of CBT plus treatment as usual (TAU) for ADHD and TAU only.[2] Patients were adults with a mean age of 35.9 years old with 69.7% male. Patients were included if they were

TABLE. Treatment effects comparing CBT plus medication versus medication alone[1]

Scoring scales[a]	Time	CBT+medication[b] vs medication from T1
ADHD-RS scores (range 0–54)	T3	20.0 vs 22.5
Inattention subscale (range 0–54)	T2	12.0 vs 13.4
	T3	12.1 vs 13.8
CAARS (range 0–78)	T2	34.0 vs 37.7
	T3	35.6 vs 38.5
	T4	34.9 vs 36.8
SAS emotional symptoms (range 20–80)	T2	31.8 vs 38.2
	T3	32.1 vs 37.4
	T4	32.7* vs 38.0
SDS emotional symptoms (range 20–80)	T2	36.9 vs 41.7
	T3	36.4 vs 41.4
	T4	36.8 vs 41.2
STAI: State Anxiety (range 20–80)	T2	38.9 vs 45.6
	T3	38.7 vs 46.5
STAI: Trait Anxiety (range 20–80)	T2	43.9 vs 50.8
ATQ (range 30–150)	T3	56.8* vs 68.6
WHOQOL-BREF: Social Domain (range 0–100)	T2	55.9 vs 52.3
	T3	58.9 vs 52.4
WHOQOL-BREF: Physical Domain (range 0–100)	T3	57.6 vs 49.2
WHOQOL-BREF: Psychological Domain (range 0–100)	T3	56.0 vs 49.7

[a] All with statistically significant differences between CBT+medication versus medication alone at time indicated, with exception of CAARS. [b] All CBT+medication outcomes from baseline (T1) $P<.01$ unless denoted by *, then $P<.05$.

18 to 65 years old, with ADHD diagnosed by a mental health professional, score ≥6, on the inattentive or the hyperactive/impulsive subscale of the adult Barkley Current Symptoms Scale (CSS, range 0–54, a higher score indicating a higher frequency of symptom), and moderate clinical severity indicated by a score of ≥4 on the Clinical Global Impression (CGI) scale (range 1–7, with 7 extremely ill). Patients were randomly assigned to the CBT (n=30; up to 15 CBT sessions over 30 weeks plus 1 CBT session at 42 weeks) or TAU (n=30; medical management alone). The primary outcome measures included the CSS and the Work and Social Adjustment Scale (WSAS), which measured the impairment in functioning in relation to a specific problem (range 0–40, higher scores indicating a more impairment). Secondary outcomes included depression and anxiety, and quality of life that were measured using the various scoring systems such as Hospital Anxiety and Depression Scale (HADS; score range 0–21, higher score indicating more symptoms of anxiety or depression). At 42 weeks, CBT+TAU showed a significant improvement in hyperactive/impulsive symptoms: CSS scores (8.8 points lower in CBT+TAU vs TAU; effect size [ES] –1.3; $P<.001$), and the Work and Social Adjustment Scale: WSAS scores (6.6 points lower in CBT+TAU vs TAU; ES –0.82; $P=.003$). For the secondary outcomes, the HADS scores were significantly lower for CBT+TAU versus TAU in both anxiety (ES –0.62; $P=.015$) and depression (ES –0.62; $P=.015$). No side effects were reported in this clinical trial. EBP

Michen Dugan, DO
Clayton Spencer, DO
Suzanne Whitney Courtney, DO
United Hospital Center Family Medicine, Bridgeport, WV

The corresponding faculty author is Suzanne Whitney Courtney, DO; suzanne.courtney@wvumedicine.org
The authors declare no conflicts of interest.

References

1. Pan MR, Zhang SY, Qiu SW, et al. Efficacy of cognitive behavioural therapy in medicated adults with attention-deficit/hyperactivity disorder in multiple dimensions: a randomised controlled trial. *Eur Arch Psychiatry Clin Neurosci*. 2022;272(2):235-255. [STEP 2]
2. Dittner AJ, Hodsoll J, Rimes KA, Russell AJ, Chalder T. Cognitive-behavioural therapy for adult attention-deficit hyperactivity disorder: a proof of concept randomised controlled trial. *Acta Psychiatr Scand.* 2018;137(2):125-137. [STEP 2]

Does beetroot juice reduce high-altitude illness?

EVIDENCE-BASED ANSWER

In healthy adults and teens, dietary nitrate supplementation in the form of beetroot juice (BRJ) does not reduce the rates of high-altitude illness (SOR: **B**, consistent, small, randomized controlled trials [RCTs]). BRJ may worsen acute mountain sickness symptoms under some conditions (SOR: **C**, small crossover RCT using a simulated altitude environment).

DOI 10.1097/EBP.0000000000002104

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

A 2016 single-blinded parallel group randomized controlled trial (RCT; n=40) examined the effects of dietary nitrate supplementation on symptoms of acute mountain sickness (AMS).[1] Participants included healthy male teenagers (mean age 16 years old) during an 11-day trek from Kathmandu (1,300 m) to Mount Everest Base Camp (5,300 m). Before selection, a health screening questionnaire was completed by the participants' parents, with no individuals excluded because of poor health. Participants in the study completed baseline physiologic testing at sea level in the United Kingdom before departure, with measurements of respiratory rate, resting blood pressure, resting and postexertion heart rate, and oxygen saturation before and after completion of a two-minute stepping exercise protocol. Participants were randomly assigned to either nitrate supplementation in the form of 70 mL of beetroot juice (BRJ) or placebo, consisting of 70 mL of concentrated blackcurrant juice, given twice daily during the climb. During the trek, after an overnight fast, physiologic measurements were recorded daily along with Lake Louise AMS questionnaire scores. No difference was noted in AMS incidence between the BRJ consumption and control groups (odds ratio [OR] 1.2; 95% CI, 0.59–2.3). At the highest altitude, 65% of trekkers met criteria for AMS, but there continued to be no difference between the treatment groups. Only 26 patients were assessed at the highest altitude (5,300 m) because of trekkers being removed due to AMS concerns. Subgroup analysis of physiological parameters showed no major differences between the two groups. Limitations to the study included enrolling only teenage males, a large amount of missing data because of patient dropout, noticeable discrepancies in taste between study drinks, and a small sample size.

A 2021 single-blinded prospective study (n=22) assessed the effect of dietary BRJ on acute AMS during a 20-day, high-altitude military expedition.[2] The participants (mean age 28 years old) were randomized to receive two 70 mL doses per day of BRJ or a calorie-matched placebo. Treatment started three days before the expedition at a baseline altitude of 44 m and was discontinued on day 17 upon reaching the highest sleeping altitude of 4,800 m. Primary outcomes included the measurement of fitness index scores and high-altitude illness–related symptoms at three predetermined altitudes (2,350 m, 3,400 m, and 4,800 m). Participants needed to be greater than 18 years old, low altitude dwellers, and physically fit for military duty. Researchers excluded climbers using acetazolamide prophylaxis. Symptoms of AMS were assessed using the 2018 Lake Louise AMS Score (LLS) and the Acute Mountain Sickness—cerebral score (AMSc), with scores greater than three and 0.7 points, respectively,

considered diagnostic for AMS. Fitness index scores, measured at baseline and maximum altitude, used the Harvard Step Test that measures heart rate recovery after a fixed step protocol, scored from zero to 100, with increasing scores consistent with improved cardiovascular fitness (score ranges >96, 68–82, and <54 consistent with excellent, average, and poor fitness, respectively). Six percent of participants (4/22) were diagnosed with AMS with no difference between the BRJ and placebo groups. Likewise, no difference was noted in LLS and AMSc scores between the two groups at the three predetermined testing altitudes. The control group fitness index decreased at 4,800 m compared with sea level (59.9 vs 67.0, $P=.003$), whereas no difference was noted in the BRJ group (61.9 vs 66.3, $P=.26$). Limitations included a small sample size and the use of a controlled, graded ascent profile designed to minimize high-altitude illness, which may have limited symptoms incidence. Also, although fitness index scores are a good surrogate for measurement of fitness, VO_2 max and time to exhaustion are considered gold standards.

A 2017, double-blinded RCT crossover study (n=20) evaluated the efficacy of BRJ supplementation on AMS.[3] Participants were actively fit men, average age 22 years old, without prior travel to an altitude over 1,500 m in the previous six months and no medical contraindications to maximal exercise testing. Participants were randomized to receive 70 mL of beetroot juice daily for six days compared or placebo separated by a minimum 10-day washout, whereupon crossover testing was completed with each group using the alternate treatment. Using a normobaric, hypoxic chamber, baseline exercise assessments were completed for all individuals in both normoxic (FiO_2 0.21, as at sea level) and hypoxic (FiO_2 0.12, as at 4,219 m) environments. Patients then initiated a six-day supplementation period. On day five, they were subjected to a six-hour hypoxic exposure in a normobaric, hypoxic chamber, during which they underwent three, 20-minute periods of submaximal exercise. The primary outcomes included patient-reported severity of high-altitude headache and AMS symptoms, as recorded by a visual analog scale and AMSc scores. With four to six hours of hypoxic testing, BRJ supplementation increased high-altitude headache (delta 10 [1, 20] mm; $P=.03$) as well as AMSc (delta 0.15 [–0.01, 0.31]; $P=.07$) compared with placebo. Subgroup analysis showed that for the five participants who experienced AMS in the placebo group measured by an AMSc >0.7, BRJ supplementation worsened headache severity (delta 26 [–3, 56] mm; $P=.07$) and AMSc scores (delta 0.46 [–0.10, 1.02]; $P=.09$). BRJ supplementation had no effect on either metric for the remaining 12 participants who experienced no AMS during the placebo phase. Limitations of the study included small sample size, artificial altitude simulation, inclusion of only men, and short duration of hypoxic exposure. EBP

Dillon Cleary, MD
Andrew Dickson, DO
Nellis Air Force Base Family Medicine Residency, Nellis Air Force Base, NV

The corresponding author is Dillon Cleary, MD; Dillon.m.cleary.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 Air Force at large, or the Department of Defense.

References

1. Hennis PJ, Mitchell K, Gilbert-Kawai E, et al. Effects of dietary nitrate supplementation on symptoms of acute mountain sickness and basic physiological responses in a group of male adolescents during ascent to Mount Everest Base Camp. *Nitric Oxide*. 2016; 60:24–31. [STEP 3]
2. Marshall AR, Rimmer JE, Shah N, et al. Marching to the Beet: the effect of dietary nitrate supplementation on high altitude exercise performance and adaptation during a military trekking expedition. *Nitric Oxide*. 2021;113-114:170-177. [STEP 2]
3. Rossetti GMK, Macdonald JH, Wylie LJ, et al. Dietary nitrate supplementation increases acute mountain sickness severity and sense of effort during hypoxic exercise. *J Appl Physiol (1985)*. 2017; 123(4):983–992. [STEP 3]

Is dietary sodium restriction superior to regular diet in hospitalized patients with heart failure to decrease length of stay?

EVIDENCE-BASED ANSWER

Sodium restriction in hospitalized adults with acute decompensated heart failure does not decrease length of stay or improve clinical signs or symptoms of heart failure. (SOR: **B**, systematic review of small RCT and small RCT).

DOI 10.1097/EBP.0000000000002081

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

In 2018, a systematic review of nine RCTs involving 479 patients with heart failure examined the effect of low salt intake on cardiovascular outcomes.[1] This systematic review included adults with acute decompensated heart failure in the inpatient setting and stable patients with chronic heart failure in the outpatient setting. Two RCTs focused on sodium restriction in patients (mean ages 54 and 60 years old) admitted with decompensated heart failure. Patients were randomly assigned to either approximately 0.8 g/day of sodium with an 800 mL fluid restriction per day compared with a control group receiving 3 to 4.5 g of sodium and a minimum of 2.5 liters of fluid intake per day until discharge or the seventh hospital day. In the other RCT, patients were restricted to 0.8 g of sodium per day compared with less than 4 grams per day. The primary outcome was mortality; secondary outcomes included length of stay and clinical stability as measured with a clinical congestion score. The clinical congestion score is a 22-point scale measuring signs and symptoms of congestion such as crackles, edema, jugular venous distention, hepatojugular reflux, New York Heart Association (NYHA) class, orthopnea, paroxysmal nocturnal dyspnea, and third heart sound where a higher score indicated worse congestion. No difference was observed in length of stay between the aggressive sodium and fluid restriction group and the control group (1 RCT, n=75; 7 vs 6 days; P=.89). No difference was observed in the clinical congestion symptom score change between the aggressive sodium and fluid restriction group and controls in hospitalized patients from baseline to three-day reassessment (1 RCT, n=75; −4.0 vs −3.4; P=.47). No difference was observed between difference in time to compensation of symptoms between the intervention group and the control group (1 RCT, n=32; 7.5 vs 6.6 days; P=.18). None of the trials examined had low risk of bias in all 7 domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data outcome, selective reporting, and other bias), and all were noted to have unclear bias in at least two domains.

A 2018 RCT (n=53) examined the effectiveness of aggressive sodium and fluid restriction in hospitalized patients with decompensated heart failure.[2] The study population included adult patients with mean age of 72 years old and 68% female with a diagnosis of heart failure with preserved ejection fraction (majority NYHA class III and IV) who were admitted to the hospital for decompensated heart failure. Most patients had hypertension, and about half had atrial fibrillation and diabetes. Approximately 80% of patients were taking furosemide, 75% a beta-blocker, 64% an angiotensin-converting enzyme inhibitor, and 27% spironolactone. Researchers excluded patients with glomerular filtration rate less than 31 mL/min, cardiogenic shock, severe valvular disease, or dementia. The intervention group received a sodium-restricted diet of 0.8 g sodium (2 g salt) and 800 mL fluids/day compared controls which received a standard diet of 4 g sodium (10 g salt) daily and unlimited fluid intake. The duration was until day 7 of hospitalization or discharge. The primary outcome was weight loss. A secondary outcome was clinical stability as measured by discontinuation of intravenous heart failure medications and improved congestion symptoms. No difference was observed in clinical stability scores between the sodium restriction and control groups at the end of the study period (−3.4 vs −3.8; P=.70). Changes in weight loss were also similar between the two groups (−1.6 kg vs −1.8 kg; P=.49). Side effects were not reported in this study. EBP

Bryan May, MD
Ethan Hall, DO
Sarah Daly, DO, FAAFP
Utah Valley Family Medicine Residency, Provo, UT

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

References

1. Mahtani KR, Heneghan C, Onakpoya I, et al. Reduced salt intake for heart failure: a systematic review. *JAMA Intern Med.* 2018; 178(12):1693-1700. [STEP 1]
2. Machado d'Almeida KS, Rabelo-Silva ER, Souza GC, et al. Aggressive fluid and sodium restriction in decompensated heart failure with preserved ejection fraction: results from a randomized clinical trial. *Nutrition*. 2018;54:111-117. [STEP 2]

In pregnant patients with a history of prior fetal growth restriction, does the addition of 81 mg aspirin reduce rates of fetal growth restriction compared with no prophylaxis?

EVIDENCE-BASED ANSWER

In patients with high risk for preeclampsia, low-dose aspirin prophylaxis reduces fetal growth restriction (FGR) if initiated at or before 16 weeks of gestation (SOR: **A,** meta-analysis of randomized controlled trials). In gravid patients with a history of fetal growth restriction, without additional risk factors for preeclampsia, aspirin prophylaxis for the prevention of recurrent FGR is not recommended (SOR: **C**, evidence-based expert opinion).

DOI 10.1097/EBP.0000000000001971

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

A 2017 meta-analysis of 45 randomized controlled trials (RCTs) (N=20,909) evaluated the effectiveness of aspirin dosing for prevention of preeclampsia and FGR in high-risk gravid patients.[2] Patient's risk factors consisted of abnormal umbilical artery Doppler, cardiovascular or endocrine disease, history of fetal growth restriction, hypertension in pregnancy, or chronic hypertension history. Patient demographics were not included. Patients received aspirin (50–150 mg per day), initiated between less than seven weeks and up to 36 weeks gestation, compared with placebo or no treatment. Two studies used dipyridamole 300 mg daily with 100 or 150 mg of aspirin. Researchers stratified some outcomes by gestational age at initiation of aspirin (greater than 16 weeks or 16 weeks or less). Aspirin prophylaxis resulted in a significant reduction in FGR (17 trials, N=2,939; relative risk [RR] 0.56; 95% CI, 0.44–0.70) when therapy was initiated at or less than 16 weeks' gestation compared with placebo and no treatment. When initiated at or before 16 weeks' gestation, 100 mg aspirin was more effective than 60 mg aspirin in reducing FGR (11 trials, N=4,311; RR 0.45; 95% CI, 0.28–0.71 vs RR 0.78; 95% CI, 0.53–1.2; *P*=.006). When aspirin was initiated after 16 weeks, no risk reduction was seen for FGR (18 trials, N=8,922; RR, 0.95; 95% CI, 0.86–1.1). Limitations of the study included inconsistent dosing of aspirin, inconsistent definitions of "high risk for preeclampsia" across the RCTs, and a lack of clear inclusion/exclusion criteria for the RCTs included.

In 2018, the American College of Obstetricians and Gynecologists (ACOG) published a consensus statement that included practice guidelines developed by an expert panel made from the Committee of Obstetric Practice and the Society for Maternal-Fetal Medicine, addressing the use of low-dose aspirin in pregnancy.[1] ACOG did not recommend the use of low-dose aspirin for the prevention of recurrent fetal growth restriction in patients without a moderate or high risk for preeclampsia because of insufficient evidence (no strength of recommendation provided). ACOG did state that low-dose aspirin initiation before 16 weeks in women with risk factors for preeclampsia may decrease the risk of fetal growth restriction (no strength of recommendation provided). EBP

Roy Wagner, DO
Katie Coble, MD
Saint Louis University (Southwest Illinois) Family Medicine Residency, O'Fallon, IL

The corresponding author is Roy Wagner; RMarshallWagner@outlook.com
The authors declared 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. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. *Am J Obstet Gynecol*. 2017; 216(2): 110–120.e6. [STEP 1]
2. ACOG Committee opinion No. 743: low-dose aspirin use during pregnancy. *Obstet Gynecol*. 2018;132(1):e44-e52. [STEP 3]

In patients with preoperative anxiety, is pharmacological treatment or acupuncture therapy more effective at reducing anxiety symptoms?

EVIDENCE-BASED ANSWER

Acupuncture may reduce preoperative anxiety compared with sham techniques, but no significant difference is seen when compared with benzodiazepine use (SOR: **B**, systematic reviews and meta-analyses, with additional randomized controlled trial [RCT]). However, acupuncture and benzodiazepine therapy together may reduce preoperative anxiety more than benzodiazepine treatment alone (SOR: **B**, RCT).

DOI 10.1097/EBP.0000000000002083

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

A 2022 systematic review and meta-analysis of 15 randomized controlled trials (RCTs) (N=1,603) examined the effect of auricular stimulation on preoperative anxiety.[1] Inclusion criteria for the systematic review included randomized clinical trials with patients from any population undergoing medical interventions under any type of anesthesia. Studies compared auricular stimulation or related interventions (auricular acupuncture, auricular acupressure, auricular electroacupuncture) with any type of pharmacological or nonpharmacological controls. Primary outcomes were measured with self-report anxiety scales including the State Trait Anxiety Inventory (STAI), Anxiety Visual Analog Scale-100 (VAS-100), the Amsterdam Preoperative Anxiety and Information Scale (APAIS), and Self-Rating Anxiety Scale (SAS). Auricular stimulation decreased anxiety scores compared with sham (8 studies; N=701; standardized mean difference [SMD] −0.72; 95% CI, −1.09 to −0.36; I^2=80%) and no intervention (4 studies; N=420; SMD −1.01; 95% CI, −1.6 to −0.45). However, no difference was found between auricular stimulation compared with benzodiazepine use (3 studies; N=158; SMD −0.05; 95% CI, −0.36 to 0.26; I^2=0%). No trials reported any serious adverse effects of auricular stimulation. Limitations of the analysis included heterogeneity regarding surgical procedures, control conditions, and effect size.

A 2020 systematic review of 12 RCTs (N=916) compared the efficacy of acupuncture therapy with sham acupuncture to reduce preoperative anxiety.[2] Studies included adult emergency and elective surgery patients undergoing general anesthesia and containing preoperative data. The treatment interventions included acupuncture, electroacupuncture, auricular acupuncture, auricular acupressure, and percutaneous electrical acupoint stimulation. Interventions in the control groups were sham acupuncture, sham acupoint, or preoperative routine nursing. Primary outcomes were measured using patient-reported scales, including the STAI scale, VAS-100, NRS (Numerical Rating Scale), HAMA (Hamilton Anxiety Scale), and Zung Self-rating Anxiety Scale (SAS). Patients who received acupuncture therapy had lower STAI-S scores (mean difference [MD] −9.07; 95% CI, −13.19 to −4.96; I^2=85%) and VAS scores (MD −1.37; 95% CI, −2.29 to −0.45; I^2=86%). No differences were found in HAMA scores between the two groups (MD −3.98; 95% CI, −12.89 to 4.92; I^2=94%). The RCTs were of moderate-to-low quality and high heterogeneity. Of the studies examined, four (80%) found no adverse events in either the acupuncture or sham groups, while one reported a 4% incidence of postoperative nausea and vomiting in acupuncture patients and a 15% incidence in the control group.

A single-site RCT (n=120) compared the effectiveness of auricular (AA) and somatic (SA) acupuncture with midazolam in reducing preoperative anxiety in patients undergoing cholecystectomy or extraperitoneal hernia repair.[3] Patients with an American Society of Anesthesia (ASA) score of more than two and patients with myofascial pain, fibromyalgia, and severe respiratory, neurologic, and cardiac disease were excluded. The primary outcome was interoperative relaxation (measured through administration of propofol and fentanyl). The secondary outcome was preoperative anxiety measured using the STAI (Italian version) before and after treatment. Patients in both acupuncture groups (SA and AA) required less propofol than the patients receiving midazolam (0.14 mg/kg/h SA vs 0.20 mg/kg/h for midazolam, P=.0019, and 0.14 mg/kg/h AA vs 0.2 mg/kg/h

midazolam, $P=.0016$). Patients receiving SA also used less fentanyl than the midazolam group (0.39 mcg/kg vs 0.28 mcg/kg, $P=.002$). No difference in fentanyl use was found between AA and PT groups. No significant differences were found between the groups when comparing STAI scores. No adverse events attributed to either form of acupuncture were reported.

A single-site RCT (n=360) compared the effectiveness of complementary and alternative treatments (CAM), including recorded guided imagery (CDRGI), acupuncture, individual guided imagery, and reflexology, in reducing preoperative anxiety with benzodiazepine treatment (BZD) alone.[4] Patients included were those undergoing undergoing bariatric, hernia, colon, cholecystectomy, and other surgery. Patients with respiratory or hemodynamic instability were excluded. Patients were randomized to one of three treatments (CDRGI, ST, and individualized CAM). CDRGI treatment involved the patient listening to a recorded relaxation and imagery script. BZD treatment included either oxazepam (10 mg) or diazepam (5–10 mg). Patients randomized to the individual CAM group were then given guided imagery, reflexology, or acupuncture with ST based on the day of the week because of practitioner availability. The primary outcome evaluated was anxiety evaluated with a 10 cm VAS before and after treatment (before entering the operating room). All patients receiving a CAM treatment demonstrated reduced anxiety VAS score (5.54 vs 2.32; $P<.0001$). Acupuncture was one of the multiple CAM treatments provided. Patients were undergoing elective surgeries, so baseline anxiety may be less. EBP

Stacie Kasper, DO
Hussain Banu, MBBS, MD
Karla Hemesath, PhD
University of Iowa Family Medicine Residency Program, Iowa City, IA

The corresponding author is Stacie Kasper; stacie-kasper@uiowa.edu.
The authors declare no conflicts of interest.

References

1. Usichenko TI, Hua K, Cummings M, et al. Auricular stimulation for preoperative anxiety—a systematic review and meta-analysis of randomized controlled clinical trials. *J Clin Anesth.* 2022;76:110581. [STEP 1]
2. Tong QY, Liu R, Zhang K, Gao Y, Cui GW, Shen WD. Can acupuncture therapy reduce preoperative anxiety? A systematic review and meta-analysis. *J Integr Med.* 2021; 19(1):20-28. [STEP 1]
3. Zanella S, Buccelletti F, Vassiliadis A, et al. Preoperative anxiety management: acupuncture vs. pharmacological treatment—a prospective study. *Eur Rev Med Pharmacol Sci.* 2022;26(3):900-905. [STEP 3]
4. Attias S, Keinan Boker L, Arnon Z, et al. Effectiveness of integrating individualized and generic complementary medicine treatments with standard care versus standard care alone for reducing preoperative anxiety. *J Clin Anesth.* 2016; 29:54-64. [STEP 3]

Does the long-term use of proton pump inhibitors increase the risk of gastric cancer among adult patients?

EVIDENCE-BASED ANSWER

Yes, use of proton pump inhibitors (PPIs) from six months to three years is associated with a higher likelihood of gastric cancer in adult patients (SOR **B**: meta-analysis of cohort and case-control studies and single cohort study). The risk of gastric cancer among patients taking PPIs may be similar to risk for those taking histamine type-2 receptor antagonists (H2RAs), and the association may be more robust in patients taking 15 or more medications (SOR **B**: cohort studies).

DOI 10.1097/EBP.0000000000002067

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

A 2022 systematic review and meta-analysis of eight cohort studies and eight case-control studies (N=2,936,935) evaluated the association between PPIs and the likelihood of gastric cancer.[1] Demographics provided in studies were very limited, with only some studies reporting average ages between 55 and 76 years old. Dosing information and type of PPIs

were not reported, but studies compared PPI users with nonusers with a follow-up time ranging from 4.2 to 7.6 years. After pooling all 16 studies, PPI use was associated with an increased likelihood of gastric cancer than PPI nonuse (odds ratio [OR] 1.8; 95% CI, 1.3–2.4, I^2=97%). The likelihood of gastric cancer was consistent throughout all periods measured with increased odds at less than one year use (10 studies, N=1,663,982; OR 2.6; 95% CI, 1.4–4.6), 1 to 3 years use (10 studies, N=2,604,903; OR 1.5; 95% CI, 1.3–1.7), and greater than three years use (8 studies, N=2,579,373; OR 1.6; 95% CI, 1.2–2.1). An increased likelihood of gastric cancers was also observed in individuals who received PPI therapy after *Helicobacter pylori* eradication (3 studies, N=77,684; OR 2.7; 95% CI, 1.8–4.0). Limitations included very high heterogeneity, lack of duration-dependent effect, and lack of reporting of type and dose of PPI.

A 2022 cohort study (n=10,012) investigated the use of PPIs and the likelihood of gastric cancer development.[2] Patients were either prescribed a PPI or H2RA (dosing information not provided), divided according to the medication duration (60, 90, 120, and 180 days) and followed for up to 11 years (median follow-up 6.6 years). The groups had no differences in sex at birth or age. Patients diagnosed with any other malignancy before the diagnosis of gastric cancer and those younger than 20 years old were excluded. After adjusting for *H. pylori* infection, a cumulative daily dose of 60 days of PPI use during a median follow-up of 6.6 years was not associated with an increased likelihood of gastric cancer compared with a similar use of H2RA (adjusted hazard ratio [aHR] 1.3; 95% CI, 0.75–2.3).

A 2017 cohort study (n=1,563,860) reported use of acid-suppressing therapies and the likelihood of site-specific stomach cancer.[3] Individuals who had a related prescription filled before the study period were excluded. Approximately 55% or patients were female with a median age reported for groups ranging from 40 to 59 years old. A subgroup of patients who received 15 or more prescriptions was identified and included 6.6% of the H2RA users and 14.7% of the PPI users. Patients were categorized by first prescription received. The first H2RA prescription was most commonly cimetidine (53.2%), nizatidine (23.8%), or ranitidine (22.7%). The first PPI prescription was most commonly omeprazole (30.9%), lansoprazole (30.6%), or pantoprazole (21.5%). No information regarding specific medications or dosages was provided. Among patients receiving 15 or more prescriptions, there was a significant greater risk for stomach cancer compared with nonusers for both the PPI users (HR 6.5; 95% CI, 4.1–10.5) and for H2RA users (HR 4.6; 95% CI, 1.8–12.1). Limitations included the censoring of controls at the time of prescription if they received an acid-suppressing drug because this could have artificially decreased gastric cancer incidence in this group overall and the focus of the study in comparing the sites of the gastric cancer instead of the medication as the primary outcome. EBP

Hinal Patel, MD
Annie Truss, MD
Jennifer Amico, MD, MPH
Department of Family Medicine and Community Health, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

The corresponding author is Jennifer Amico; amicojr@rwjms.rutgers.edu.
The authors have no conflicts of interest to declare.

References

1. Peng TR, Wu TW, Li CH. Association between proton-pump inhibitors and the risk of gastric cancer: a systematic review and meta-analysis. *Int J Clin Oncol*. 2023;28(1):99-109. [STEP 2]
2. Gong EJ, Bang CS, Kim DK, Lee JJ, Baik GH. Use of proton pump inhibitors and the risk for the development of gastric cancers: a nationwide population-based cohort study using balanced operational definitions. *Cancers (Basel)*. 2022; 14(20):5172. [STEP 3]
3. Wennerström ECM, Simonsen J, Camargo MC, Rabkin CS. Acid-suppressing therapies and subsite-specific risk of stomach cancer. *Br J Cancer*. 2017;116(9):1234-1238. [STEP 3]

What is the optimal oral glycemic control medication for patients with diabetic kidney disease?

EVIDENCE-BASED ANSWER

In patients with diabetes and chronic kidney disease, sodium–glucose cotransporter 2 (SGLT-2) inhibitors reduce the risk of major adverse cardiovascular events and renal events when compared with glucagon-like peptide 1 (GLP-1) receptor agonists or placebo (SOR: **A**, meta-analysis of randomized controlled trials). SGLT-2 inhibitors should be used in diabetic patients with an estimated glomerular filtration rate less than or equal to 20 mL/min/1.73 m^2 regardless of glycemic control (SOR: **C**, expert opinion).

DOI 10.1097/EBP.0000000000002092

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

A 2021 meta-analysis of 13 randomized controlled trials (N=32,949) compared the benefits of sodium–glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists with placebo in adults with type 2 diabetes and chronic kidney disease (CKD).[1] Patients were adults with estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2. In six trials with an SGLT-2 inhibitor, patients assigned treatment received canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, or sotagliflozin, and follow up period ranged from 16 to 50 months. In seven trials with GLP-1 receptor agonists, patients assigned treatment received albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, or semaglutide (subcutaneously or orally) with follow-up ranging from 19 to 65 months. Doses and frequency of medications varied across trials with all comparing with placebo. Major adverse cardiac events (MACE) included cardiovascular death, myocardial infarction, and stroke. Renal outcomes included end-stage renal disease (ESRD), renal death and cardiovascular death, and reduced kidney function, defined as a decrease in eGFR of between 30% and 50% or as a doubling of creatinine. After pooling all six trials (N=20,106), SGLT-2 inhibitors led to a risk reduction in both MACE (risk ratio [RR] 0.85; 95% CI, 0.75–0.96) and renal events (RR 0.68; 95% CI, 0.59–0.78) compared with placebo. Conversely, GLP-1 RAs (N=7,534) did not significantly reduce the risk of MACE (RR 0.91; 95% CI, 0.80–1.04) or renal events (RR 0.86; 95% CI, 0.72–1.03) compared with placebo. No harms of intervention were reported. Limitations included possible randomization failures and definitions of renal outcomes that were not consistent across trials.

The American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO) produced a consensus, evidence-based report on diabetes management in the setting of chronic kidney disease.[2] The organizations recommend that metformin be used in patients with eGFR of 30 mL/min/1.73 m^2 or more and that SGLT-2 inhibitors be used for patients with eGFR of 20 mL/min/1.73 m^2 or less, independent of glycemic control because of benefits for reduced of CKD progression, heart failure, and ASCVD. EBP

Suzanne Clarke, MD
Cecil Brown, MD
Zachary Greenlee, MD
Russell Reeves, MD
Marquette Family Medicine Residency, Marquette, MI

The corresponding author is Suzanne Clarke, MD; Suzanne.clarke@mghs.org.
The authors declare no conflicts of interest.

References

1. Yamada T, Wakabayashi M, Bhalla A, et al. Cardiovascular and renal outcomes with SGLT-2 inhibitors versus GLP-1 receptor agonists in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and network meta-analysis. *Cardiovasc Diabetol*. 2021; 20(1):14. [STEP 1]
2. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care*. 2022; 45(12):3075–3090. [STEP 5]

Does universal syphilis rescreening in the third trimester improve neonatal outcomes?

EVIDENCE-BASED ANSWER

Universal rescreening for syphilis in the third trimester decreases the incidence of congenital syphilis and is cost-effective (SOR: **B**, 1 theoretical cohort study, 3 retrospective cohort studies). All pregnant patients should be screened for syphilis at intake and again in the third trimester (SOR: **C**, expert opinion).

DOI 10.1097/EBP.0000000000002062

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

A 2018 cost-effectiveness analysis of repeat third trimester syphilis screening used a theoretical cohort of 3.9 million pregnant patients with an annual syphilis prevalence rate of just over four per 100,000 based on 2013 U.S. Centers for Disease Control (CDC) and U.S. census data estimates.[1] The model demonstrated clear cost-benefit when including downstream costs and improved neonatal outcomes, with 41 fewer neonatal syphilis cases, 73 fewer intrauterine fetal demises, and 27 fewer neonatal and infant deaths, with a cost savings of $52 million. An aggregate increase of 4,000 quality-adjusted life-years across the cohort was noted. The authors noted that the CDC reported a rate of primary and secondary syphilis among U.S. women 15 to 44 years old in 2021 of 7.3 per 100,000, so the effect sizes noted in this study might have been an underestimation of the benefit.

A 2017 retrospective cohort study linked cases of congenital syphilis with maternal syphilis screening records in Florida and Louisiana between 2013 and 2014 (n=710) to evaluate effectiveness of syphilis screening to prevent congenital syphilis.[2] Third trimester screening was defined as taking place after 27 weeks' gestation and 30 days or more before delivery. Among the 76 women who screened negative in the first two trimesters, rescreening and effective treatment in the third trimester prevented a further 30 cases of congenital syphilis, above and beyond the 470 cases prevented by screening in the first or second trimester. Most syphilis cases were identified in pregnancies of Black, Hispanic, and foreign-born patients, highlighting racial and socioeconomic disparities in syphilis burden in the United States.

A 2018 retrospective cohort study used New York City Department of Health and Mental Hygiene data from 2010 to 2016 to examine patient-, provider-, and system-level factors contributing to congenital syphilis.[3] Among pregnant patients, 578 cases of syphilis were identified and linked to 68 cases of congenital syphilis. Among 22 congenital syphilis cases who had nonreactive testing on early screening, 15 cases lacked third trimester rescreening even though most patients would have been considered high risk per the current CDC and the U.S. Preventive Services Taskforce (USPSTF) guidelines. One syphilitic stillbirth and one infantile death occurred among the 68 congenital syphilis cases.

In a 2021 retrospective cohort study, the Arizona Department of Health Services used statewide surveillance data study to identify missed opportunities in prevention of congenital syphilis.[4] Between January 1, 2017 and June 30, 2018, 57 congenital syphilis cases were identified. The study authors estimate that 17 (29.8%) of these cases may have been prevented using third trimester rescreening policies, which included nine patients screened late in prenatal care, seven patients who seroconverted after an initial nonreactive test, and one patient reinfected after early treatment.

In 2018, the USPSTF updated their recommendation statement on early prenatal syphilis screening to a grade A recommendation.[5] Although the USPSTF evidence review primarily focused on early prenatal screening, it did address the lack of new studies to offer a recommendation for interval rescreening in the third trimester. Of note, the statement affirmed that rescreening at 28 weeks' gestation in high-risk patients was endorsed by the CDC, American College of Obstetricians and Gynecologists, and American Academy of Pediatrics. An updated USPSTF evidence review is currently underway and may offer additional guidance in the near future. As of 2018, 12 states require by law third trimester screening with all pregnancies, and many departments of public health independently recommend universal third trimester screening based on local syphilis prevalence. EBP

Corey Walsh, MD
Henry Colangelo, MD, MPH
Allie Lindbloom, MD
Roxanne Radi, MD, MPH
University of Colorado Family Medicine Residency, Denver, CO

The corresponding author is Henry Colangelo; henry.colangelo@cuanschutz.edu.
The authors declare no conflicts of interest.

References

1. Hersh AR, Megli CJ, Caughey AB. Repeat screening for syphilis in the third trimester of pregnancy: a cost-effectiveness analysis. *Obstet Gynecol*. 2018;132(3):699-707. [STEP 3]
2. Matthias JM, Rahman MM, Newman DR, Peterman TA. Effectiveness of prenatal screening and treatment to prevent congenital syphilis, Louisiana and Florida, 2013-2014. *Sex Transm Dis*. 2017;44(8):498-502. [STEP 3]
3. Slutsker JS, Hennessy RR, Schillinger JA. Factors contributing to congenital syphilis cases—New York City, 2010-2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(39):1088-1093. [STEP 3]
4. Sykes KJ, Scranton RA, Villarroel L, Anderson BV, Salek S, Stall J. Using surveillance data to respond to an outbreak of congenital syphilis in Arizona through third-trimester screening policies, 2017-2018. *Public Health Rep*. 2021;136(1):61-69. [STEP 3]
5. US Preventive Services Task Force, Curry SJ, Krist AH, Owens DK, et al. Screening for syphilis infection in pregnant women: US preventive Services task force reaffirmation recommendation statement. *JAMA*. 2018;320(9):911-917. [STEP 5]

Does supplementation with probiotics affect BMI in obese adults?

EVIDENCE-BASED ANSWER

Probably. Probiotics, such as *Lactobacillus sp*. and *Bifidobacterium sp*., likely reduce BMI in obese adults (SOR: **B**, umbrella meta-analyses of randomized controlled trials [RCTs] with low quality). Probiotic supplementation also may reduce BMI in women with a diagnosed food addiction who eat a restricted calorie diet (SOR: **C**, small RCT). *Saccharomyces boulardii* superoxide dismutase therapy does not appear to result in a significant reduction of BMI (SOR: **C**, small RCT).

DOI 10.1097/EBP.0000000000002088

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

A 2022 umbrella meta-analysis of 29 meta-analyses of randomized controlled trials (RCTs) (N=14,366) investigated the effects of probiotics use on body mass index (BMI) and other obesity indices (eg, body weight, waist circumference) among obese adults.[1] Patients were adults who were 18 years and older; no other demographics and inclusion/exclusion criteria were presented by the authors. The intervention group received probiotics that were various strains of 11 microorganisms (dosage not provided); the most commonly used were *Lactobacillus sp.* and *Bifidobacterium sp*. The control group included patients receiving placebo. Study durations ranged from 4 to 28 weeks. The primary outcomes included BMI. A significant reduction in BMI was observed for the probiotic group compared with the control group (29 meta-analyses, N=14,366; effect size [ES] –0.21; 95% CI, –0.30 to –0.13; I^2=83.0%).

A 2022 double-blind RCT (n=62) examined the impact of probiotic supplementation on various obesity indices, including BMI.[2] Patients were women (mean age 34 years old), with an obese BMI (defined as 30.0–39.99 kg/m^2) who ate a restricted calorie diet. All patients had a diagnosis of food addiction. Researchers excluded patients who were pregnant, lactating, past menopause, or had any history of cancer, cardiovascular disease, or other chronic illness. Patients were randomized to twice daily multiprobiotic supplements (n=31) or placebo supplements (n=31) in conjunction with a standardized calorie-restricted diet. The probiotic supplement contained a mixture of three *Lactobacillus* species and three *Bifidobacterium* species. The primary outcomes included BMI measured at baseline, 6 weeks, and 12 weeks. After 12 weeks, the probiotic supplementation group had a significant decrease in BMI compared with the placebo group (intervention, –2.5 kg/m^2 vs control, –1.1 kg/m^2; $P<.001$). The study's generalizability was limited by its restrictive inclusion and exclusion criteria.

A 2021 RCT (n=25) assessed the effects of *Saccharomyces boulardii*–derived superoxide dismutase supplementation on body mass and composition.[3] This study was not included in the umbrella meta-analysis above. Patients were obese adults with a mean age of 54 years and 68% female. Researchers enrolled outpatients 30 to 65 years old with a BMI between 30 and 35 kg/m^2. Researchers excluded anyone with evidence of liver, heart, or kidney disease. The

intervention group (n=12) received capsules containing *S boulardii,* superoxide dismutase, and inactive compounds, whereas the control group (n=13) received a placebo of the inactive compounds. Both groups took the capsules for 60 days at mealtimes. Outcomes included BMI. Within the intervention group, a significant decrease in BMI was seen at 60 days compared with baseline (mean difference [MD] –0.97; 95% CI, –1.7 to –0.25). However, there was no significant difference in BMI between the two groups (MD –0.62; 95% CI, –1.7 to 0.43). This study was limited by short study duration, high percentage of females, and a small sample size. EBP

Raye Reeder, MD
Catherine Lower, DO
Nile McCullough, MD
OU-TU School of Community Medicine, Family and Community Medicine, Tulsa, OK

The corresponding author is Raye Reeder, DO; Raye-Reeder@ouhsc.edu.
The authors declare no conflicts of interest.

References

1. Musazadeh V, Zarezadeh M, Ghalichi F, et al. Anti-obesity properties of probiotics; a considerable medical nutrition intervention: findings from an umbrella meta-analysis. *Eur J Pharmacol.* 2022:928:175069. [STEP 1]
2. Narmaki E, Borazjani M, Ataie-Jafari A, et al, The combined effects of probiotics and restricted calorie diet on the anthropometric indices, eating behavior, and hormone levels of obese women with food addiction: a randomized clinical trial. *Nutr Neurosci.* 2022;25(5):963-975. [STEP 2]
3. Rondanelli M, Miraglia N, Putignano P, et al. Effects of 60-day *Saccharomyces boulardii* and superoxide dismutase supplementation on body composition, hunger sensation, pro-antioxidant ratio, inflammation and hormonal lipo-metabolic biomarkers in obese adults: a double-blind, placebo-controlled trial. *Nutrients*. 2021;13(8):2512. [STEP 3]

Is quetiapine an effective treatment for generalized anxiety disorder?

EVIDENCE-BASED ANSWER

Quetiapine reduces anxiety scores and improves remission rates in patients with generalized anxiety disorder (GAD) more than placebo (SOR: **A**, two meta-analysis studies of randomized controlled trials [RCTs]). However, the drug has a high side effect rate—37% for quetiapine versus 5.4% for placebo (SOR: **A**, one meta-analysis study of RCTs).

DOI 10.1097/EBP.0000000000002091

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

A 2019 systematic review and network meta-analysis of 89 RCTs (N=25,411) analyzed 22 different pharmacological therapies compared with placebo in the treatment of adults with GAD.[1] Of these 89 RCTs, four trials (N=1,804) compared quetiapine and placebo. Patients were adult outpatients 18 years old and older (mean age 48 years old) with 65% female patients. The trials were included if they compared at least two commercially available pharmacological options versus placebo and reported change from baseline on a scale intended to measure anxiety. Researchers excluded trials of refractory GAD, patients with comorbidities other than depression, trials with relapse prevention, or discontinuation designs. The intervention groups received quetiapine XR 30 mg, 50 mg, or 300 mg for 8 to 9 weeks. The primary outcome for efficacy was the change in the Hamilton anxiety scale (HAM-A) and the odds ratio for study discontinuation due to side effects, withdrawal, or loss to follow-up as measures for acceptability. HAM-A evaluated the presence and degree of severity of anxiety symptoms ranging from a total score of 0 to 56 (0–17 [mild], 18–24 [mild to moderate], 25–30 [moderate to severe], and 31–56 [very severe]). Quetiapine was significantly more efficacious (4 RCTs, N=1,804; mean difference [MD] −3.6; 95% CI −4.8 to −2.4) but poorly tolerated (4 RCTs, N=1,804; odds ratio [OR] 1.4; 95% CI 1.2–1.8) compared with placebo. This study was limited by a broad range of settings across the trials.

A 2010 Cochrane systematic and meta-analysis of 11 RCTs (N=4,144) examined the efficacy and tolerability of second-generation antipsychotic for anxiety

disorders, including quetiapine for the treatment of generalized anxiety disorder (GAD).[2] Of these 11 RCTs, 4 trials (N=2,262) compared quetiapine and placebo. Patients were adults 18 years and older with anxiety disorders including GAD. Patients with a primary or secondary diagnosis of another axis I or axis II disorder were excluded. The quetiapine monotherapy groups were compared with placebo and antidepressants (paroxetine, escitalopram). The quetiapine groups were randomized in flexible doses ranging from 25 mg to 400 mg/day (mean doses between 147–168 mg/day) and in fixed doses of 50 mg, 150 mg, or 300 mg/day. Duration was categorized as short term (up to 12 weeks), medium term (3–6 months), and long term (longer than 6 months). The primary outcome was determined by the number of patients with an at least 50% reduction in the HAM-A from the baseline. Secondary outcomes were remission (HAM-A total score of 7 or less) and relapse of anxiety symptoms. The quetiapine group significantly responded better to treatment (4 RCTs, N=2,262; OR 2.2; 95% CI 1.1–4.5), more remission (4 RCTs, N=2,262; OR 1.8; 95% CI 1.1–3.1), and less relapse (1 RCT, n=433; OR 0.18; 95% CI 0.10–0.30) compared with placebo. Adverse events (extrapyramidal side effects, weight gain, or sedation) in the quetiapine group were significantly higher compared with the placebo group (37% vs 5.4%; $P<.05$). Limitations included incomplete reporting, selective reporting, and the lack of details of randomization method and blinding procedures. In addition, all trials were sponsored by the pharmaceutical company producing the study drug. EBP

Socorro Shelton, MD
Radhika Chang, MD
Salman Elgharbawy, MD
Pamela Hunter-Reach, MD
Martin Richard, MD
Southern Illinois University Family Medicine Residency Program, Carbondale, IL

The corresponding author is Socorro Shelton; sshelton77@siumed.edu.
The authors declare no conflicts of interest.

References

1. Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. *Lancet*. 2019;393(10173):768-777. [STEP 1]
2. Depping AM, Komossa K, Kissling W, Leucht S. Second-generation antipsychotics for anxiety disorders. *Cochrane Database Syst Rev*. 2010;(12):CD008120. [STEP 1]

Do symptom-triggered versus fixed, scheduled doses of benzodiazepines improve outcomes for hospitalized patients with alcohol withdrawal?

EVIDENCE-BASED ANSWER

Unclear. In hospitalized patients at low risk for alcohol withdrawal, symptom-triggered treatment reduces therapy duration by 60 hours and cumulative benzodiazepine dose by 10 mg lorazepam equivalents compared with scheduled fixed-dose regimens (SOR: **A**, systematic review of randomized controlled trials). However, in patients hospitalized with alcohol withdrawal syndrome and acute mental illness or complications from nutrition or electrolyte imbalances, symptom-triggered versus fixed-dose therapy may be associated with a higher cumulative benzodiazepine dose and might increase the risk of intubation and intensive care unit admission (SOR: **B**, retrospective cohort study). Symptom-triggered benzodiazepine dosing may be considered for managing inpatients with moderate alcohol withdrawal symptoms (SOR: **C**, evidence-based guideline).

DOI 10.1097/EBP.0000000000002052

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

A 2019 systematic review and meta-analysis of six randomized controlled trials (RCTs; N=676) compared outcomes for symptom-triggered versus fixed-dose benzodiazepine therapy for alcohol withdrawal.[1] The studies were from inpatient detoxification settings (3 RCTs, N=281), general medical hospitals (2 RCTs, N=230), and outpatient treatment facilities (1 RCT, n=165), located in the United States (3 RCTs, N=331), Europe (2 RCTs, N=331), and India (1 RCT, n=63). The patients were predominantly male patients (87%) with average ages ranging from 38.6 to 51.7 years old. Most studies excluded patients with significant medical and psychiatric comorbidities. Studies defined symptom-triggered therapy as any regimen using a standardized alcohol withdrawal scale to determine medication dose while fixed-dose therapy involved administering an initial benzodiazepine medication regardless of symptoms followed (in 5 of 6 RCTs, N=511) by as needed symptom-based dosing. Medications used included chlordiazepoxide, lorazepam, and oxazepam, with most studies using the same drug for both symptom-triggered and fixed-dose regimens; one trial (n=47) used symptom-triggered lorazepam and fixed-dose diazepam. Outcomes were mortality, delirium, seizures, treatment duration, and total benzodiazepine dose (in mg lorazepam equivalent). With symptom-triggered versus fixed-dose therapy, the treatment duration was shorter (3 RCTs, N=281; mean difference [MD] −60.4 hours; 95% CI, −81.1 to −39.7 hours) and patients required less benzodiazepine (6 RCTs, N=643; MD −10.5 mg lorazepam equivalent; 95% CI, −13.9 to −7.1 mg). There were not enough events among the studies to determine the superiority of either approach on mortality, seizure, or delirium. The study was limited by moderate-to-high heterogeneity (I^2=66%–91%), inability to assess for publication bias, and inclusion of a significant proportion of patients who were at low risk for alcohol withdrawal symptoms.

A 2022 retrospective cohort study evaluated medical record data from 93 Veterans Health Administration hospitals to explore the association between various benzodiazepine dosing strategies and hospital course among 6,938 medical inpatients with alcohol withdrawal syndrome (AWS).[2] Patients were mostly male (97%), White race/ethnicity (72%), and hospitalized either with an acute mental illness (51%) or complications associated with nutrition, electrolyte, or acid-base disorders (44.9%). Benzodiazepine regimens were symptom-triggered (42%), fixed-dose (41%), and front-loading (initial benzodiazepine dose followed by fixed-dose, symptom-triggered, or continuous IV infusion; 17%). Lorazepam was the most used benzodiazepine (80%), followed by chlordiazepoxide (40%), and diazepam (15%); patients often received more than one benzodiazepine. Primary outcomes were cumulative benzodiazepine use (in mg diazepam equivalent), intubation rates, and need for intensive care unit (ICU) admission during the initial 10 days of hospitalization, adjusted for patient demographics and clinical characteristics, inpatient diagnoses, and hospital location. Symptom-

triggered compared with fixed-dose therapy was associated with higher cumulative amounts of benzodiazepines (MD 26.4 mg diazepam equivalent; 95% CI, 9.4–43.4 mg) and higher odds of intubation (odd ratio [OR] 1.5; 95% CI, 1.1–2.1) and ICU admission (OR 1.7; 95% CI, 1.5–2.0). Limitations of the study included reliance on International Classification of Diseases, Ninth Revision (ICD)-9 coding to identify AWS, leading to possible underidentification. In addition, the study data lacked Clinical Institute Withdrawal Assessment (CIWA) scores (used to assess alcohol withdrawal severity), and cross-over between the different dosing schedules was not evaluated.

A 2020 consensus and evidence-based guideline from the American Society of Addiction Medicine recommended symptom-triggered benzodiazepine dosing for managing inpatients with moderate alcohol withdrawal symptoms (no SOR or evidence grade provided).[3] The guideline recommended that clinicians use CIWA scores to assess alcohol withdrawal symptom severity and observed that symptom-triggered dosing reduced cumulative benzodiazepine use and shortened treatment duration. However, the guideline acknowledged the possible harmful side effects of symptom-triggered management stating that requiring patients to experience withdrawal symptoms may contribute to progressive worsening severity because of increased neuronal activity in each episode of withdrawal. EBP

Ivy Sandquist, MD
Jennifer Tiskus, MD
Jasper Kennedy, MD
Mari Yamamoto, PhD
Department of Family Medicine, University of Washington, Seattle, WA

The corresponding author is Mari Yamamoto; mariy@uw.edu.
The authors declare no conflicts of interest.

References

1. Holleck JL, Merchant N, Gunderson CG. Symptom-triggered therapy for alcohol withdrawal syndrome: a systematic review and meta-analysis of randomized controlled trials. *J Gen Intern Med*. 2019;34(6):1018–1024. [STEP 2]
2. Steel TL, Malte CA, Bradley KA, Hawkins EJ. Benzodiazepine treatment and hospital course of medical inpatients with alcohol withdrawal syndrome in the Veterans Health Administration. *Mayo Clin Proc Innov Qual Outcomes*. 2022; 6(2):126–136. [STEP 3]
3. The ASAM clinical practice guideline on alcohol withdrawal management [published correction appears in *J Addict Med*. 2020;14(5):e280]. *J Addict Med*. 2020;14(3 suppl 1):1–72. [STEP 5]