May 2023

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

May 2023
Volume 26 | Number 5

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FPIN
Family Physicians Inquiries Network

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

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

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

EVIDENCE-BASED PRACTICE

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STATEMENT OF PURPOSE

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

EDITORIAL POLICY

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.

Less is more for community-acquired pneumonia

Dinh A, Ropers J, Duran C, et al. Discontinuing β-lactam treatment after three days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial [published correction appears in *Lancet*. 2021 Jun 5;397(10290):2150]. *Lancet*. 2021;397(10280): 1195-1203. doi: 10.1016/S0140-6736(2100313-5).

DOI 10.1097/EBP.0000000000001594

A double-blind, randomized, placebo-controlled non-inferiority trial compared three days of β-lactam treatment plus an additional five-day course of antibiotic or five days of placebo in adult patients admitted to a noncritical care unit for moderately severe community-acquired pneumonia. Average age of patients was 73 years old, and 39% in each group required oxygen. Severity of illness was balanced between groups using the Pneumonia Severity Index (a 5-tiered risk categorization based on clinical factors). All patients had a new infiltrate on CT or chest x-ray during diagnosis. Patients who were clinically stable after three days of β-lactam treatment (oral or intravenous amoxicillin plus clavulanate or parenteral third-generation cephalosporin) received five additional days of oral amoxicillin 1 g plus clavulanate 125 mg three times a day or matched placebo. Clinical stability was defined as temperature 37.8°C or lower, heart rate below 100 beats per min, respiratory rate below 24 breaths per min, arterial oxygen saturation of 90% or higher, systolic blood pressure of 90 mmHg or higher, and normal mental status. The primary outcome was cure (clinical improvement of symptoms and lung examination findings and no need for additional antibiotics) 15 days after first antibiotic use. In the per-protocol analysis, 78% of patients in the placebo group were cured at day 15 compared with 68% of patients in the amoxicillin–clavulanate group (difference of 9.4%; 95% CI, –0.15 to 20; meeting the 10% noninferiority threshold). No difference in cure rates was noted between groups stratified by severity of illness. Adverse events were similar between both groups (14% in placebo vs 19% in β-lactam group). C-reactive protein, procalcitonin, and sputum culture analysis were not required in this study. Loss to follow-up was only 3%.

Current U.S. guidelines for adults with community-acquired pneumonia recommend no less than five days of antibiotic treatment, whereas European guidelines recommend seven days of treatment.[1,2]

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 IDSA guidelines and French guidelines 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	Yes	Clinically meaningful	No

Bottom line: A three-day course of β-lactam antibiotics may adequately treat hospitalized patients with moderate-to-severe community-acquired pneumonia, but practice change requires additional studies comparing this with a treatment regimen commonly used in the United States.

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References

1. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2019;200(7):e45-e67.
2. Woodhead M, Blasi F, Ewig S, et al. Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections–full version. *Clin Microbiol Infect.* 2011;17(-suppl 6):E1-E59.

Walking for postpartum depression

Pentland V, Spilsbury S, Biswas A, Mottola MF, Paplinskie S, Mitchell MS. Does walking reduce postpartum depressive symptoms? A systematic review and meta-analysis of randomized controlled trials. *J Womens Health (Larchmt)*. 2021. doi:10.1089/jwh.2021.0296

DOI 10.1097/EBP.0000000000001694

A 2021 systematic review and meta-analysis of randomized controlled trials (RCTs) sought to determine if walking decreases postpartum depressive symptoms. RCTs were included if they were studies of postpartum women with a child up to 24 months old and who were categorized as depressed at baseline using the validated Edinburgh Postpartum Depression Scale (EPDS) with a score of ≥13. Five studies with 242 patients (all with mild-to-moderate depression as measured by the EPDS; mean age of 29 years old) were included in the meta-analysis. The primary intervention had to be exercise in which walking was the sole or principal (>50%) modality. The control groups included "usual care" (3 trials) and "nonintervention" or weekly "group social support" session (1 trial each). The endpoint (change in EPDS score) was evaluated at 12 weeks (4 trials) to six months (1 trial). Pooled analysis showed a total mean difference of –4.01 (95% confidence interval [CI], –7.18 to –0.84) in the EPDS score, suggesting that walking decreases postpartum depressive symptoms. However, in the narrative summary, the authors mentioned that a clinically significant difference in the EPDS score is a change of four (or more) points, but neglect to address the fact that the 95% CI substantially overlaps this minimal clinically important difference (MCID). Beyond that, there was significant heterogeneity (I^2=86%) at least in part because of trial inclusion of mixed aerobic activity (undefined), mixed intensity of activity (optimal not defined), and trials where patients were also taking antidepressants.

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 "postpartum depression," "walking," and "exercise" to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: This systematic review and meta-analysis falls short of demonstrating practice-changing validity and clinical significance for suggesting that walking improves symptoms of postpartum depression. Furthermore, it is troubling that the authors very briefly touch on the topic of MCID (an outcome that their meta-analysis does not achieve with a 95% CI), but then promote the statistical significance in the resultant change in a depression score.

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The authors declare no conflicts of interest.

Choose apixaban to anticoagulate frail elderly patients with atrial fibrillation

Kim DH, Pawar A, Gagne JJ, et al. Frailty and clinical outcomes of direct oral anticoagulants versus warfarin in older adults with atrial fibrillation: a cohort study. Ann Intern Med. 2021;174(9):1214-1223. doi:10.7326/M20-7141.

DOI 10.1097/EBP.0000000000001663

This retrospective cohort study compared the safety of three direct oral anticoagulants (DOACs: dabigatran, rivaroxaban, and apixaban) with warfarin in Medicare beneficiaries of various levels of frailty with atrial fibrillation using 1:1 propensity score matching analysis. Patients were 65 years old or older, filled a prescription for a DOAC or warfarin, had no oral anticoagulant exposure in the

previous 183 days, had a diagnosis code of atrial fibrillation, and were continuously enrolled in Medicare parts A, B, and D. Patients were excluded if they had missing key demographic data, received hospice care, resided in a nursing facility at the time of drug initiation, had other indications for anticoagulation, or had a contraindication to a DOAC or warfarin. The primary outcome was the composite endpoints of death, ischemic stroke, or major bleeding. The outcome was measured on the DOAC group as a whole and subdivided based on frailty, determined by the claims frailty index (CFI). Nonfrailty was defined as CFI <0.15, prefrailty as CFI >0.15 to 0.24, and frailty as ≥ 0.25. Each DOAC grouping was matched and compared based on combined comorbidity score, CHA_2D_2VASc, and modified HAS-BLED score.

In the dabigatran/warfarin cohort (n=158,730; median follow-up [f/u] of 72 days), the event rate (ER) was 63.5 per 1000 person-years (PYs) for dabigatran and 65.6 per PY for warfarin (hazard ratio [HR] 0.98; 95% CI, 0.92–1.05). In the rivaroxaban/warfarin cohort (n=275,944; median f/u 82 days), the ER per PY was 77.8 for rivaroxaban and 83.7 for warfarin (HR 0.98; 95% CI, 0.94–1.02). Both dabigatran and rivaroxaban were associated with a significant reduction in hazard ratios for the nonfrail population only (HR 0.81; 95% CI, 0.68–0.97; and HR 0.88; 95% CI, 0.77–0.99, respectively).

In the apixaban/warfarin cohort (n=218,738; median f/u 84 days), the ER per PY was 60.1 for apixaban and 92.3 for warfarin (HR 0.68; 95% CI, 0.65–0.72). For nonfrail, prefrail, and frail patients, HRs were 0.61 (95% CI, 0.52–0.71), 0.66 (95% CI, 0.61–0.70), and 0.73 (95% CI, 0.67–0.80), respectively. Apixaban was the only DOAC to reduce the hazard of death, ischemic stroke, or major bleeding compared with warfarin among all frailty groups.

Methods

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

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

Bottom line: Apixaban was superior to warfarin in treatment of atrial fibrillation in the elderly patients of all frailty classifications. The other two DOACs were only superior to warfarin in the nonfrail elderly patients with atrial fibrillation. The study was limited by being a retrospective cohort study and these finding should be confirmed with controlled prospective trials. Frailty is not often considered as a measurable trait. No comparison of foregoing anticoagulation was noted in the frail elderly in comparison with anticoagulation.

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The authors declare no conflicts of interest.

Carrying lactation to new heights? Baby carriers may increase breastfeeding at six months

Little EE, Cioffi CC, Bain L, Legare CH, Hahn-Holbrook J. An infant carrier intervention and breastfeeding duration: a randomized controlled trial. Pediatrics. 2021;148(1): e2020049717. doi:10.1542/peds.2020-049717.

DOI 10.1097/EBP.0000000000001709

This is a randomized two-arm, parallel-group study of 100 low-income Latinx women to assess the impact of an infant carrier on breastfeeding and expressed human milk feeding and exclusive human milk feeding rates. Women were randomly allocated to receive an infant carrier, plus instruction on proper use, during their prenatal visits (n=50) or placed on a "waitlist" control group. Breastfeeding rates were assessed at six weeks, three months, and six months postpartum. Parents in the intervention group were more likely to be breastfeeding or feeding expressed human milk at six months than parents in the control group (68% vs 40%, respectively; $P=.02$), but not exclusive human milk feeding (49% intervention vs 26% control, $P=.06$). At six weeks and three months, respectively, no significant

differences were found in rates of exclusive breastfeeding (66% intervention vs 49% control, $P=.20$; and 45% intervention vs 40% control, $P=.59$) or in rates of breastfeeding/expressed human milk feeding (78% intervention vs 81% control, $P=.76$; and 66% intervention vs 57% control, $P=.34$).

Although strengths to this study (randomized controlled design and a well-defined population cohort) are present, multiple limitations are also noted. These include small sample size (low power), relatively high attrition rate at the six-month assessment, very specific population cohort with higher-than-average breastfeeding baseline rates, and a much higher rate of dropouts from the younger population demographic.

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, USPSTF, AAP, AAFP, and USAFP with the terms "baby carrier" OR "breastfeeding" to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: This study demonstrates possible benefit of baby carrier use on the outcome of breastfeeding or exclusive human milk consumption at six months postpartum. However, the numerous limitations of the study impair the generalizability of the study findings as well as the external validity of the findings (low power). Although the authors feel that providing the baby carriers would be cost-effective in the low-income population demographics, a potential barrier to implementation is present.

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The authors declare no conflicts of interest.

Benefits of urate-lowering therapy in asymptomatic hyperuricemia

Tien YY, Shih MC, Tien CP, Huang HK, Tu YK. To Treat or Not to Treat? Effect of Urate-Lowering Therapy on Renal Function, Blood Pressure and Safety in Patients with Asymptomatic Hyperuricemia: A Systematic Review and Network Meta-Analysis. J Am Board Fam Med. 2022; 35(1):140-151. doi:10.3122/jabfm.2022.01.210273

DOI 10.1097/EBP.0000000000001734

This network meta-analysis investigated the effects of various urate-lowering drugs on serum uric acid level, renal function, and blood pressure in patients with asymptomatic hyperuricemia (AH). Patients with symptomatic hyperuricemia were not included in the reviewed trials. From a starting pool of 777 studies, 13 randomized controlled trials (RCTs) totaling 2,842 patients were included in the final meta-analysis; the number of patients included in the individual RCTs ranged from 28 to 1,070 and all of the included trials went through extensive review before final decision to include in the meta-analysis. Primary outcomes included short-term (<6 months) and long-term (>6 months) effects of medications on the following: serum uric acid level, renal function, and blood pressure. Regarding urate-lowering effect, eight of the 13 RCTs were analyzed for the short-term effect while three studies were analyzed for the long-term urate-lowering effects. Short- and long-term renal function outcomes were evaluated by five and three RCTs, respectively. Blood pressure outcomes were evaluated by three studies in the short term and four in the long term. The authors included six trials (1,269 patients) when analyzing the secondary outcomes, which were adverse effects of the medications. The interventions included use of allopurinol, benzbromarone, and febuxostat at different doses compared with placebo. The authors used a P-score, which was derived from *P*-values, as a descriptor to indicate the likelihood of one treatment being better than another treatment. A large

P-score (>0.90) suggested a treatment was more effective. The analysis found that in patients with AH, benzbromarone and allopurinol had the best urate-lowering effects in both the short- and the long-term follow-up. Febuxostat had the best results for lowering systolic blood pressure in the short term and diastolic blood pressure in the long term, whereas allopurinol only had significant long-term systolic blood pressure–lowering effect. Allopurinol was shown to have a protective effect of the kidneys with a P-score of 1.000 in the long-term study group.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching Uptodate with the terms "asymptomatic hyperuricemia" 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	No
Change in practice	No	Clinically meaningful	No

Bottom line: In patients with asymptomatic hyperuricemia, urate-lowering therapy may prove to be beneficial for cardiovascular and renal disease risk reduction. Unfortunately, currently no screening guidelines for asymptomatic hyperuricemia are present; also, a direct causal association does not exist between hyperuricemia and the above mentioned diseases. Further research and development of screening guidelines are needed.

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The authors declare no conflicts of interest.

Peppermint oil treatment for irritable bowel syndrome: a randomized placebo-controlled trial

Nee J, Ballou S, Kelley JM, et al. Peppermint Oil Treatment for Irritable Bowel Syndrome: A Randomized Placebo-Controlled Trial. Am J Gastroenterol. 2021;116(11):2279-2285. doi: 10.14309/ajg.0000000000001395

DOI 10.1097/EBP.0000000000001818

This double-blinded randomized placebo-controlled trial compared the efficacy of peppermint oil versus placebo for the treatment of irritable bowel syndrome (IBS) symptoms. The trial focused on patients with IBS as diagnosed by the Rome IV criteria with moderate-to-severe IBS based on the validated IBS Severity Scoring System (IBS-SSS). The IBS-SSS is a composite score of severity of abdominal pain, frequency of abdominal pain, severity of abdominal distention, dissatisfaction with bowel habits, and quality of life. Each of the five measures is rated from 0 to 100 with combined scores ranging from 0 to 500, with higher scores indicating greater severity. Mild scores are generally accepted as <175, moderate 175 to 300, and severe >300. A minimal clinically important difference with the IBS-SSS score is accepted to be ≥50 points. The trial's primary outcome was a mean change in the IBS-SSS from baseline to the study's end at six weeks of treatment duration.

Patients were randomized with a 2:1 ratio between the placebo (n=87) and the treatment (n=46) groups. Patient demographics and baseline characteristics were similar between trial groups with patients' mean age in the early 40s, mostly White (86% in placebo group, 76% in peppermint oil group), and women (74% in each). An intention-to-treat analysis of the primary outcome found a substantial mean improvement in the IBS-SSS score for both placebo and peppermint oil groups, with no significant difference in scores between the two groups (−100.3 vs −90.8, respectively; P=.97). Furthermore, 70% of patients in both the peppermint oil group and the placebo group showed at least a 50-point increase

on the IBS-SSS, suggesting that both the intervention and the control groups had equal benefits for most patients. Both the treatment and the placebo arms had a total of 16 patients dropout, with eight withdrawing secondary to adverse events that mostly included belching (10.9% vs 2.3%; *P*=.048) and reflux/heartburn (26.1% vs 11.5%; *P*=.031), respectively. It should be noted that because of the 2:1 trial design, the dropout rate for the intervention group was twice that of the placebo group.

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

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching UptoDate and PubMed with the terms IBS and peppermint oil, to find additional literature to place this research into the context of current clinical practice.

Bottom line

Peppermint oil is not superior to placebo for improving IBS symptoms based on the validated IBS-SSS scoring system, although approximately 70% of patients obtain clinically significant symptom improvement with either therapy. However, peppermint oil use has significantly more side effects than placebo.

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Is there sustained weight loss after discontinuation of GLP-1 agonist for obesity treatment?

EVIDENCE-BASED ANSWER

No. While patients lose weight while taking a GLP-1 agonist in a dose-dependent and duration-dependent fashion, they will tend to regain weight if the medication is stopped (SOR: **A**, multiple randomized controlled trials). It is unclear whether or when the rebound weight might attain the pre-treatment baseline.

DOI 10.1097/EBP.0000000000001786

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

A multisite randomized controlled trial (RCT; withdrawal study design, n=803) examined the effect on patient weight of weekly subcutaneous semaglutide versus placebo after an initial 20 weeks of semaglutide treatment. Patients were overweight adults (body mass index [BMI] >27 kg/m^2) with a comorbid condition and adults with obesity (BMI >30 kg.m^2) with at least one self-reported unsuccessful dietary effort to lose weight.[1] Those with an HgA1c of 6.5% or higher or a self-reported change in body weight of more than 5 kg within 90 days of screening were excluded. All patients received once-weekly subcutaneous semaglutide, starting at 0.25 mg, and increased every four weeks to maintenance dose of 2.4 mg once weekly by week 16 and continued at that dose to week 20. At week 20, patients were randomized in a 2:1 ratio to continue the 2.4 mg weekly dose or a placebo and followed for 48 weeks. All patients received lifestyle interventions to include calorie deficit diet and increased physical activity. From week 20 to 48, the continuation group had greater weight loss than the placebo group (–7.9% vs 6.9%; mean difference [MD] –14.8%; 95% CI, –16% to –13.5%). Gastrointestinal side effects were more prevalent in the semaglutide continuation group than the placebo group (41.9% vs 26.2%; no *P* value given).

A 2017 multicenter, randomized, placebo-controlled trial (N=2,254) examined the effectiveness of the GLP-1 agonist liraglutide for weight management and prevention of development of diabetes.[2] Patients were adults with prediabetes and BMI >30 kg/m^2 or a BMI >27 kg/m^2 with comorbid conditions. The intervention group (n=1,505) received liraglutide 3.0 mg subcutaneously once daily while the control group (N=749) received a matched placebo over the study duration of 160 weeks. While both groups lost weight by the end of the study, weight loss for the intervention group was significantly more than the placebo group (body weight MD –4.3%; 95% CI, –4.9% to –3.7%). At the end of the 160-week study period, all medications were stopped and patients were followed for an additional 12 weeks. At the end of this 12-week interval, the intervention group still had a larger weight loss than the control group, although the magnitude was decreased (body weight MD –3.2%; 95% CI, –4.3% to –2.2%). Study limitations included loss of approximately half of the study participants (47% in liraglutide group and 55% in control group) and the lack of longer follow-up after cessation of the intervention.

A phase II randomized, placebo-controlled, double-blind trial (n=297) examined the effectiveness of the GLP-1 agonist efpeglenatide on weight loss, change in BMI, waist circumference, and improved metabolic laboratory markers, compared with placebo.[3] Patients were nondiabetic adults from multiple countries, ages 18 to 65 years old with a BMI 30 kg/m^2 or higher or a BMI of 27 kg/m^2 or higher and a comorbid medical condition. Those with a BMI of 42 or greater, patients with drug-induced obesity, patients with known diabetes, and patients with HgA1c >6.5% were excluded. Patients were divided into five arms: efpeglenatide 4 mg once weekly, efpeglenatide 6 mg once weekly, efpeglenatide 6 mg once every two weeks, efpeglenatide 8 mg every two weeks, or placebo. All those assigned to a drug intervention arm were started on efpeglenatide 4 mg during week 1 and up-titrated to their respective intervention dose in week 2. All efpeglenatide treatment treatment arms resulted in a significant reduction in body weight while on therapy compared with placebo: 4 mg once weekly, –6.8 kg (95% CI, –8.4 to –5.1); 6 mg once weekly, –7.4 kg (95% CI, –9.1 to –5.7); 6 mg once every two weeks, –6.7 kg (95% CI, –8.4 to –5.1); 8 mg once every two weeks, –7.5 kg (95% CI, –9.2 to –5.8). Side effects of the medication occurred in 86.4% of all study participants. Discontinuation rates for the treatment groups were 25% to 31% and 20% for the

placebo group. Most discontinuations were due to mild-to-moderate side effects. Limitations of this study were the small sample size, the short duration of the study, no longitudinal follow-up for any treatment arm, and the study administrators did not require the participants to document or adhere to lifestyle changes that were discussed in the study proposal. EBP

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The authors declare no conflicts of interest.

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

References

1. Rubino D, Abrahamsson N, Davies M, et al; STEP 4 Investigators. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA.* 2021;325(14):1414-1425. [STEP 2]
2. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet.* 2017;389:1399-1409. [STEP 3]
3. Pratley RE, Kang J, Trautmann ME, et al. Body weight management and safety with efpeglenatide in adults without diabetes: a phase II randomized study. *Diabetes Obes Metab.* 2019;21:2429-2439. [STEP 2]

Do produce prescription programs improve outcomes in adults with type two diabetes mellitus?

EVIDENCE-BASED ANSWER

Produce prescription programs may result in modest improvements in hemoglobin A1c, minimal improvement in BMI, and an increase in fruit and vegetable intake, but not in blood pressure or cholesterol indices (SOR: **B**, meta-analysis of randomized control trials and quasi-experimental noncontrolled trials).

DOI 10.1097/EBP.0000000000001847

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

A 2021 meta-analysis of 13 studies (N=1,039; 3 randomized control trials; 9 pre/poststudies with and without control groups; and 1 retrospective case control study) evaluated the impact of produce prescription programs on health behavior and cardiometabolic risk factors.[1] The studies included adult patients (mean age 45–60 years old) referred into the program by a healthcare professional; half the patients experienced food insecurity, and 75% were obese or had hypertension or type 2 diabetes. Pregnant or breastfeeding women were excluded. The primary outcomes were changes in hemoglobin A1c (HbA1c) (5 studies), BMI (3 studies), blood pressure (BP) (4 studies), lipids (2 studies), and change in intake of fruits and vegetables, as reported by patients (9 studies). Nine studies provided food subsidies to patients; the other four used mobile food vans or food pantries. The median follow-up duration was six months, while three studies ranged from 12 to 18 months. Most of the studies were completed in the United States. The produce prescription programs improved BMI by 0.6 kg/m^2 (3 studies, N=215; 95% CI, –1.1 to –0.2) and HbA1c (5 studies, N=1,064; mean difference –0.8%; 95% CI, –1.6 to –0.1), but not systolic BP, diastolic BP, LDL, HDL, or triglycerides. The programs increased fruits intake of 0.8 servings per day (95% CI, 0.2–1.4) and increase in vegetable intake of 0.5 servings/day (95% CI, 0.0–1.1). Limitations included study methodology heterogeneity, a small sample size in studies that measured cardiometabolic risk factors, and recall bias in patients reporting fruit and vegetable intake.

A 2021 prospective cohort study (n=97) in a hospital-based primary care clinic evaluated the impact of a produce prescription program on uncontrolled diabetes and cardiovascular risk outcomes.[2] The study included adult diabetic patients (mean age 54 years old, 81.4% Hispanic/Latinx), with HbA1c 7% or greater, and a BMI of 25 kg/m^2 or greater; 70.1% had hyperlipidemia, and 78.4% had hypertension. Patients received vouchers for seven months to use at a farmers' market after attending monthly one-hour long sessions on diabetes self-management education (DMSE) over six months. The primary outcomes were changes in HbA1c, BP, BMI, and knowledge about nutrition. The patients' HbA1c and weight were obtained at enrollment and at the end of seven months, BMI was calculated, and BP was obtained from the chart or the last DMSE session. Knowledge of nutrition was assessed at the beginning of the study and the end using a five-question survey. Vouchers were tracked with unique number identifiers to determine whether and when patients had used their vouchers. HbA1c was obtained on 85.6% (n=83) of patients, BP data on 92.8% (n=90), and BMI on 91.8% (n=89), while 57.7% completed the follow-up survey. After the seven-month produce prescription program, HbA1c decreased by 1.3% (10.3% vs 9.0%, $P<.001$) but resulted in no change in BMI, systolic BP, or diastolic BP. Voucher redemption decreased overtime, as did DMSE attendance, with only 45% completing all seven sessions. No significant increase was observed in fruit and vegetable intake during the study. Voucher redemption was not associated with BMI but was associated with lower HbA1c, and higher BP, possibly due to variations in BP measurement. Limitations included low participation in DMSE sessions, lack of a control group, an under-resourced clinic setting limiting follow-up survey data, and the authors were unable to determine whether the study participants consumed the produce. EBP

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References

1. Bhat S, Coyle DH, Trieu K, et al. Healthy food prescription programs and their impact on dietary behavior and cardiometabolic risk factors: a systematic review and meta-analysis. *Adv Nutr.* 2021;12(5):1944-1956. [STEP 2]
2. Veldheer S, Scartozzi C, Bordner CR, et al. Impact of a prescription produce program on diabetes and cardiovascular risk outcomes. *J Nutr Educ Behav.* 2021;53(12):1008-1017. [STEP 3]

Is ibuprofen as effective as acetazolamide at preventing acute mountain sickness?

EVIDENCE-BASED ANSWER

Ibuprofen is slightly less effective than acetazolamide in preventing acute mountain sickness (AMS) at elevations most commonly encountered in the United States but may be as effective at very high-altitude ascents (SOR: **B**, small randomized, noninferiority trial and small, randomized controlled trial [RCT]). Ibuprofen is currently recommended as a second-line medication for the prevention of AMS (SOR: **C**, expert guideline).

DOI 10.1097/EBP.0000000000001841

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

A 2018 double-blind, noninferiority randomized controlled trial (RCT) (n=92) assessed the effectiveness of ibuprofen versus acetazolamide for prevention of acute mountain sickness (AMS).[1] Patients included healthy adults (18–65 years old) hiking to an elevation of 3,800 m at White Mountain, California. Patients who lived at or who had recently been at altitudes of 1,280 m or higher were excluded. Patients who were actively taking either medication before study initiation or had a previous history of severe AMS, such as high-altitude cerebral edema or pulmonary edema, were also excluded. Before their ascent, researchers randomized patients to receive ibuprofen (600 mg 3 times daily, started 4 h before ascent) or acetazolamide (125 mg twice daily, started the night before ascent). The primary outcome was the AMS incidence as defined by presence of headache and a Lake Louise Questionnaire (LLQ; range 1–12, with higher scores for worsening symptoms) score of three or greater. Results were inconclusive but trended toward ibuprofen being inferior to acetazolamide in preventing AMS (mean difference [MD] 11%; 95% CI –11% to 34%), with the 95% CI including both a MD of 0% and the noninferiority margin of 26%.

A 2010 double-blind RCT (n=265) examined the effect of ibuprofen versus acetazolamide on high-altitude headache (HAH) incidence.[2] Patients included healthy adults (18–65 years old) climbing the approach trail to Mount Everest with end altitude of 4,928 m. Exclusion criteria included Nepalese ethnicity, recent altitude exposure above study baseline altitude, and any symptoms of active AMS before initiation of intervention. Researchers randomized patients into three groups, each receiving three times daily dosing of medication that started on the day before ascent: ibuprofen 600 mg, acetazolamide 85 mg, or placebo. The primary outcome was HAH incidence using the LLQ (which includes a question on headache presence and severity). Secondary outcomes included incidence of AMS (LLQ score ≥3 with presence of headache). No difference in headache incidence was noted between the two intervention groups. In an intention-to-treat analysis, ibuprofen and acetazolamide were similarly effective at preventing AMS (incidence: acetazolamide 18.8%, ibuprofen 13.7%, placebo 28.6%; $P=.03$). Limitations included a small study size (did not reach target size at 80% power) and a high dropout rate (approximately 20% because of missed doses and previous use of both medications). In addition, the study population started at a high baseline altitude (~4,300 m) that could have introduced selection bias and limit generalizability.

The 2019 Wilderness Medical Society (WMS) issued Clinical Practice Guidelines for Prevention and Treatment of AMS with evidence-based recommendations on AMS prophylactic medications.[3] The WMS gave acetazolamide a 1A recommendation (strong, high-quality evidence) for AMS prophylaxis in travelers at moderate to high risk (those rapidly ascending to extreme altitudes [>3,800 m] or who have a previous history of AMS). Ibuprofen received a 2B recommendation (weak, moderate-quality evidence) for AMS prevention in persons with contraindications or poor side effect tolerance to acetazolamide. EBP

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

References

1. Burns P, Lipman GS, Warner K, et al. Altitude sickness prevention with ibuprofen relative to acetazolamide. *Am J Med.* 2019;132(2):247-251. [STEP 2]
2. Gertsch JH, Lipman GS, Holck PS, et al. Prospective, double-blind, randomized, placebo-controlled comparison of acetazolamide versus ibuprofen for prophylaxis against high altitude headache: the Headache Evaluation at Altitude Trial (HEAT). *Wilderness Environ Med.* 2010;21(3):236-243. [STEP 2]
3. Luks AM, Auerbach PS, Freer L, et al. Wilderness medical society clinical Practice guidelines for the prevention and treatment of acute altitude illness: 2019 update. *Wilderness Environ Med.* 2019;30(4):S3-S18. [STEP 5]

Does head CT imaging assist in the diagnosis of an adult with syncope?

EVIDENCE-BASED ANSWER

No. Only 1.2 to 3.8% of head CT scans performed on patients with syncope have clear diagnostic utility. (SOR: **A**, systematic review and meta-analysis observational studies) The most common cause of syncope, vasovagal syncope, can be diagnosed by history and physical examination alone (SOR: **C**, 1 cross-sectional, observational study).

DOI 10.1097/EBP.0000000000001846

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 17 cohort studies (N=3,361) evaluated the number of adult patients with transient loss of conscience followed by spontaneous recovery who had CT scans of the head performed and the percentage of those who had serious intracranial conditions.[1] The studies spanned from 1982 to 2016 and included 1669 ED patients and 1,289 hospitalized patients. Of the included studies, two were prospective cohort studies and 15 were retrospective chart reviews. Of the ED patients with syncope, 54% underwent a head CT and 3.8% had an underlying acute intracranial condition. Of hospitalized patients with syncope, 45% underwent head CT and 1.2% had serious acute intracranial conditions. The number needed to screen to identify an intracranial condition was 26 for ED patients and 83 for hospitalized patients. Limitations of this review included individual studies conducted on different populations and substantial heterogeneity in patients chosen to have a head CT.

A 2017 systematic review and meta-analysis of 16 cohort trails (N=6,944), which included 11 retrospective chart reviews and five prospective cohort studies, examined the prevalence of neurological studies and their diagnostic yield in assessing patients with syncope.[2] The review collected data from studies spanning 1970 to 2015 which reported the use of EEG, CT, MRI, and carotid ultrasound in evaluating syncope. CT scan was ordered in 57% of the 4,250 patients who qualified for the meta-analysis. Abnormalities were noted for 12% of CT scans; however, almost all abnormalities were believed not to be relevant to syncope. The individual studies reported a diagnostic yield of 1.2% for CT. When defining results as new and informative rather than abnormal, only one CT scan throughout the entire study cohort provided a diagnosis believed likely to be the cause of syncope. The review was of moderate quality because the definition of syncope varied somewhat among studies.

A 2022 cross-sectional, observational study of 90 consecutive patients (more than 12 years old) presenting with syncope, compared the utility of head imaging (CT/MRI) versus nonimaging modalities (eg, physical examination, history, EKG) on finding the etiology of syncope.[3] Overall, 36% (n=33) of the study population received a head CT/MRI, but only 24% (n=8) of the CT head tests had abnormal results. However, the authors noted that these abnormal results did not assist diagnosing the cause of syncope. The most common cause of syncope in the study, vasovagal syncope (68%), could be diagnosed by history and physical examination. The authors concluded head CT did not help assist in the diagnosis of an adult with syncope. The quality of this study was low due to a small patient population, no clear criteria for which modalities should be used, and not all patients receiving the same diagnostic testing. EBP

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References

1. Viau JA, Chaudry H, Hannigan A, Boutet M, Mukarram M, Thiruganasambandamoorthy V. The yield of computed tomography of the head among patients presenting with syncope: a systematic review. *Acad Emerg Med.* 2019;26(5): 479-490. [STEP 1]
2. Pournazari P, Oqab Z, Sheldon R. Diagnostic value of neurological studies in diagnosing syncope: a systematic review. *Can J Cardiol.* 2017;33(12):1604-1610. [STEP 1]
3. Uppoor RB, Patel K. Syncope: diagnostic yield of various clinical investigations. *Cureus*. 2022;14(3):e23596. [STEP 3]

Does point of care ultrasonography help determine the cause of acute dyspnea in adults?

EVIDENCE-BASED ANSWER

In the emergency department setting, point of care ultrasound (POCUS) is helpful for determining the etiology of acute dyspnea, particularly in patients with acute decompensated heart failure, with a positive likelihood ratio (LR+) of 4.8 to 8.6 and a negative likelihood ratio (LR–) of 0.13 to 0.19. (SOR: **A**, meta-analyses and consistent randomized controlled trial [RCT]). POCUS is also helpful for diagnosing pneumonia (LR+ 17, LR– 0.26) (SOR: B, RCT).

DOI 10.1097/EBP.0000000000001805

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

A 2018 systematic review and meta-analysis of seven prospective cohort studies (N=1,856) examined the accuracy of early point of care ultrasound (POCUS) for the diagnosis of acute decompensated heart failure (ADHF) in patients presenting to the emergency department (ED) with undifferentiated dyspnea.[1] All studies reported on the sensitivity and specificity of B-lines. Each study also used at least one additional diagnostic test such as chest radiography (CXR), brain natriuretic peptide (BNP), N-terminal-pro hormone BNP, or echocardiography. The criterion reference for ADHF diagnosis was medical records review by at least two expert physicians who were blinded to the POCUS data. Sonographers were blinded to the results of the additional diagnostic tests. Ultrasounds were performed by ED physicians, ED residents, ultrasound fellows, medical students, and cardiologists. The sensitivity of POCUS for the diagnosis of ADHF was 83% (95% CI, 66–92%) and specificity was 84% (95% CI, 72–91%). The positive likelihood ratio (LR+) was 4.8, and the negative likelihood ratio (LR–) was 0.19. A subanalysis of physician-only sonographers (excluding studies involving medical students and residents) across five of the seven studies (N=1,385) found POCUS for the diagnosis of ADHF had a sensitivity of 89% (95% CI, 80–94%) and specificity of 83% (95% CI, 63–94%).

A meta-analysis of six cohort studies (N=1,827) examined accuracy of POCUS and CXR for diagnosing ADHF in adult patients with acute dyspnea presenting to the ED.[2] Patients who were treated with diuretics before presentation to the ED were excluded. All adult patients received POCUS and CXR. In five of the six studies, experts reviewed medical records as the reference standard and the remaining study used a combination of echocardiogram, BNP, and CXR as the reference standard. CXR had a sensitivity of 73% and specificity of 90% (LR+ 7.3; LR– 0.3), and POCUS had a sensitivity of 88% and specificity of 90% (LR+ 8.6; LR– 0.14) for diagnosing ADHF. Applying a hierarchical summary receiver operating characteristic curve model to compare the two modalities, POCUS was more sensitive than CXR (sensitivity ratio 1.2; 95% CI, 1.1–1.3) and specificity was equivalent (specificity ratio 1.0; 95% CI, 0.90–1.1).

A prospective randomized controlled trial (RCT) examined the effectiveness of POCUS integration on diagnostic reasoning.[3] Three clinical case scenarios describing acute dyspnea presentations were

assigned randomly to 117 emergency or critical care physicians responding to an email study invitation. Participating physicians were randomized to one of three groups, receiving clinical data only, lung ultrasound videos only, or both to interpret and evaluate. Participants rated the diagnostic probability of eight possible diagnoses on a scale of 0 (unlikely, definitely not diagnosis) to 10 (definite diagnosis). The number of uncertain diagnoses, defined as a rating of 3 to 7, in each of the three study groups and the average frequency of POCUS use by each physician (less than once a week, at least once a week, daily) were included in a multivariate analysis. Data from 31 (29%) respondents were excluded as incomplete. The odds for an uncertain diagnosis was lower in the ultrasound videos only group (odds ratio [OR] 0.48; 95% CI, 0.27–0.84) and both group (OR 0.47; 95% CI, 0.27–0.83) compared with the group receiving clinical data only. This study was limited by participation bias, small numbers, and use of a subjective diagnostic scale.

A RCT examined the accuracy of POCUS and auscultation by stethoscopes in the evaluation of dyspnea.[4] Emergency room physicians trained in use of stethoscopes and POCUS were randomly assigned to use either POCUS or stethoscope in the evaluation of patients presenting to the ED for dyspnea. Patients were excluded if younger than 18 years, had a diagnosis of acute coronary syndrome, required intubation, had low POCUS image quality, or had hypotension. Sixty patients presenting to the ED over 2 months were included. Diagnostic accuracy was defined using Spearman correlation coefficients between the preliminary diagnoses of the emergency physicians and the final discharge diagnoses. The reference standard for the final discharge diagnosis was a clinical determination based on the consultations from the relevant clinics or the decision of the emergency medicine physicians. Diagnostic accuracy with POCUS for CHF was 90% with a sensitivity of 1.00 (95% CI, 0.75–1.00), specificity of 0.80 (95% CI, 0.51–0.95), yielding LR+ 5.0 while a negative test essentially ruled out the diagnosis. Diagnostic accuracy with stethoscopes for CHF was 87% with a sensitivity of 0.89 (95% CI, 0.65–0.98), specificity of 0.82 (95% CI, 0.48–0.97), LR+ 4.9, and LR– 0.13. Diagnostic accuracy with POCUS for pneumonia was 90% with a sensitivity of 0.75 (95% CI, 0.36–0.96), specificity of 0.95 (95% CI, 0.75–1.00), LR+ 17, and LR- 0.26. Diagnostic accuracy with stethoscopes for pneumonia was 86.7% with a sensitivity of 0.73 (95% CI, 0.39–0.72), specificity of 0.95 (95% CI, 0.72–1.00), LR+ 14, and LR- 0.29. There were no differences between the utility parameters for POCUS or stethoscope examinations. Examiners being unblinded potentially affected performance. EBP

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References

1. McGivery K, Atkinson P, Lewis D, et al. Emergency department ultrasound for the detection of B-lines in the early diagnosis of acute decompensated heart failure: a systematic review and metaanalysis. *CJEM*. 2018;20(3):343-352. [STEP 1]
2. Maw AM, Hassanin A, Ho PM, et al. Diagnostic accuracy of point-of-care lung ultrasonography and chest radiography in adults with symptoms suggestive of acute decompensated heart failure: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(3):e190703. [STEP 1]
3. Pontis E, Claret PG, Markarian T, et al. Integration of lung ultrasound in the diagnostic reasoning in acute dyspneic patients: a prospective randomized study. *Am J Emerg Med.* 2018;36(9):1597-1602. [STEP 2]
4. Özkan B, Ünlüer EE, Akyol PY, et al. Stethoscope versus point-of-care ultrasound in the differential diagnosis of dyspnea: a randomized trial. *Eur J Emerg Med.* 2015;22(6): 440-443. [STEP 2]

Does vitamin A improve mortality and morbidity in children with measles?

EVIDENCE-BASED ANSWER

In children two years old and younger diagnosed with measles, vitamin A 200,000 IU daily for two consecutive days reduces overall mortality. The two-dose regimen also decreases the incidence of croup and diarrhea (SOR: **A**, systematic review and meta-analysis of randomized controlled trials [RCTs]). When the same two dose regimen is used as a supplement every 4 to 6 months for healthy children 6 months to 5 years old, vitamin A is associated with a 50% reduction in the incidence of measles cases (SOR: **A**, meta-analysis of RCTs). The World Health Organization endorses vitamin A for all acute cases of measles, even in countries where measles is not usually severe (SOR: **C**, consensus statement).

DOI 10.1097/EBP.0000000000001771

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

A 2011 systematic review of eight randomized controlled trial (RCTs; N=2,574) compared the efficacy of vitamin A with placebo in improving mortality and preventing pneumonia or other complications in children with measles.[1] Studies included children <15 years old infected with measles in either hospital or community settings. Most of the studies took place in Africa, with the exception of two in Japan and England. The quality of evidence overall was moderate, with heterogeneity acting as the major limiting factor. Children in the vitamin A group were given vitamin A 200,000 IU daily for two consecutive days versus an oral placebo liquid, in addition to supportive care for both groups. Vitamin A reduced overall mortality in children younger than 2 years old (relative risk [RR] 0.21; 95% CI, 0.07–0.66). However, it did not reduce overall mortality in children older than two years old. Regarding morbidity, the vitamin A group across all ages had a decreased incidence of croup (RR 0.53; 95% CI, 0.29–0.89), a one-day reduction in duration of fever (mean difference [MD] –1.01; 95% CI, –1.89 to –0.13), a two-day reduction in duration of diarrhea (MD –1.92; 95% CI, –3.4 to –0.44), and a 15% reduced incidence of diarrhea (RR 0.85; 95% CI, 0.82–0.87). No differences were observed in pneumonia morbidity. Limitations included heterogeneity of studies, variance in the case-fatality rate of different areas, and lack of follow-up after hospital discharge.

A 2017 meta-analysis of 47 RCTs and cluster RCTs (N=1,223,856) evaluated the effect of synthetic vitamin A supplementation versus placebo in reducing mortality and morbidity in children in the community setting, which included analysis of measles incidence and mortality.[2] Studies included healthy, nonhospitalized children 6 months to 5 years old. The studies were multicontinental with both urban and rural representation. The quality of evidence overall was moderate to high. Children in the vitamin A groups received 50,000 to 200,000 IU daily for two consecutive days every 4 to 6 months for an average of 12 months, compared with placebo supplementation. While a 12% reduction in risk of all-cause mortality for the vitamin A group (RR 0.88; 95% CI, 0.83–0.93) was observed, no difference was observed in mortality for measles alone. However, six of the studies (N=19,566) identified a 50% reduction in incidence of measles in the vitamin A group (RR 0.50; 95% CI, 0.37–0.67), which may have contributed to reduced all-cause mortality. Limitations included a lack of reporting of measles-specific mortality and underreporting of implementation data of study-specific interventions.

The WHO has endorsed treating children with measles with vitamin A since 1987. Its updated 2017 position paper on measles advises administering vitamin A to children with measles immediately on diagnosis and then repeated the next day at the following dosages: 50,000 IU for infants <6 months, 100,000 IU for infants 6 to 11 months, and 200,000 IU for children 12 months or older (strong recommendation, consensus statement).[3] EBP

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

References

1. Yang HM, Mao M, Wan C. Vitamin A for treating measles in children. *Cochrane Database Syst Rev.* 2011;(4): CD001479. [STEP 1]
2. Imdad A, Mayo-Wilson E, Herzer K, Bhutta ZA. Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age. *Cochrane Database Syst Rev.* 2017;3(3):CD008524. [STEP 1]
3. Measles vaccines: WHO position paper – April 2017. Note de synthèse de l'OMS sur les vaccins contre la rougeole – avril 2017. *Wkly Epidemiol Rec*. 2017;92(17):205-227. [STEP 3]

In patients with non-neuropathic cancer-related pain, does gabapentin provide additional palliative pain control as an adjunct to opioid therapy?

EVIDENCE-BASED ANSWER

In nonspecific cancer-related pain, gabapentin as an adjunct to opioid therapy leads to moderately lower opioid doses with similar pain relief (SOR **B**; randomized controlled trial and cohort study). In cancer-related bone pain, gabapentin added to opioids is associated with a decrease in pain at rest and with movement (SOR **C**; case series).

DOI 10.1097/EBP.0000000000001730

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

A 2016 double-blinded randomized controlled trial (n=60) compared opioid needs and adverse effects between combination treatment with gabapentin plus oxycodone extended release (ER) and monotherapy with oxycodone ER in cancer-related pain.[1] The trial included adults 40 to 75 years old referred to a pain clinic in China with severe cancer pain from multiple cancer types, including colorectal, lung, prostate, and gastric; the specific types of cancer pain were not reported. Patients with severe liver or renal disease, an inability to eat or drink, or prior opioid use were excluded. No significant differences were observed in age, weight, or cancer types between the two groups. Patients rated pain on a 0 to 10 visual analog scale (VAS), and researchers titrated medications to a goal VAS of three or less. The control group received oxycodone ER 10 mg twice daily plus placebo. The intervention group received the same initial oxycodone ER dose plus gabapentin increased over three days to 300 mg three times daily and then adjusted in 300 mg increments every three days up to 2,700 mg total daily dose if the VAS score was greater than three. The average gabapentin dose was not reported. If the maximum dose of gabapentin was reached and VAS was not at goal, the researchers increased the oxycodone ER dose to achieve VAS of three or less. The titration protocol for oxycodone ER was not reported. Patients were followed at one week and then at one, three, and six months. The primary outcome was average daily dose of oxycodone ER, and the secondary outcome was adverse effects from treatment. No significant difference was observed in daily average oxycodone dose at one week and one month; however, daily average dose was significantly lower in the intervention group at three months (33 mg vs 58 mg; $P<.001$) and six months (51 vs 73 mg; $P<.001$). Drowsiness was similar between the groups, whereas nausea and vomiting (10 patients vs 18 patients; $P=.038$) and constipation (16 patients vs 29 patients; $P<.001$) were significantly less prevalent in the intervention group.

A 2021 prospective cohort study (n=74) examined the analgesic efficacy and adverse effects of combining oral gabapentin with intrathecal morphine compared with intrathecal morphine monotherapy.[2] Researchers included adults in China undergoing intrathecal delivery system for cancer pain of at least an eight on a 0-10 numerical rating scale (NRS) related to multiple types of cancer, including lung, pancreatic, colon, and gastric. Exclusion criteria were current gabapentin or pregabalin use, current chemotherapy or radiotherapy, or severe kidney disease. No difference was observed in age, sex, or cancer type between the two groups. In the combination group, gabapentin was up-titrated every three days as tolerated to 900 mg per day; the average daily dose was 644 mg. In both combination and monotherapy

groups, intrathecal morphine was then titrated to an NRS score of less than three. The primary outcomes were NRS score and daily dose of intrathecal morphine, and the secondary outcome was adverse effects from treatment. At three months, both groups noted a decrease in NRS score, but no significant difference was observed in the score decrease between both groups (–5.7 in the combination group and –6.3 in the monotherapy group; $P=.096$). The daily dose of morphine in the combination group was significantly lower than in the monotherapy group at three months (3.5 vs 4.6 mg; $P=.007$). The prevalence of at least one adverse effect, including somnolence, nausea, vomiting, and dizziness, was similar between groups (79% in the combination group and 73% in the monotherapy group; $P=.49$).

A 2008 prospective case series (n=6) in Italy explored the analgesic efficacy of the addition of gabapentin to opioid therapy for incident pain from bone metastases.[3] Incident bone pain was defined as pain with movement or related to posture. Patients rated pain on a 0-10 scale, and opioid treatment (specific agents were not reported) resulted in an average score of 3.2 at rest. The mean daily oral morphine equivalent dose was 180 mg. Incident pain was still significant with scores ranging from six to 10 (average not reported). Patients then received gabapentin with doses ranging from 100 to 200 mg three times daily. The primary outcome of mean incident pain score over five days improved to 3.7 with the addition of gabapentin, which was sustained for three months. Mean pain at rest also improved to a reported score of 0.6 (statistical analysis was not reported for either outcome). Adverse effects of somnolence, nausea, and vomiting were noted in half of the patients. EBP

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References

1. Chen DL, Li YH, Wang ZJ, Zhu YK. The research on long-term clinical effects and patients' satisfaction of gabapentin combined with oxycontin in treatment of severe cancer pain. *Medicine (Baltimore)*. 2016;95(42):e5144. [STEP 2]
2. Teng L, Dai J, Shao H, et al. Gabapentin enhances the antinociceptive effect of intrathecal morphine in refractory cancer pain patients. *Support Care Cancer*. 2021;29(12):7611-7616. [STEP 3]
3. Caraceni A, Zecca E, Martini C, Pigni A, Bracchi P. Gabapentin for breakthrough pain due to bone metastases. *Palliat Med.* 2008;22(4):392-393. [STEP 4]

Among elderly people with squamous cell carcinoma, is cryotherapy an effective treatment alternative to standard wide excision?

EVIDENCE-BASED ANSWER

Maybe. Cryotherapy is associated with a low recurrence rate when used in low-risk, nonmetastatic lesions less than 2 cm in diameter (SOR: **C**, systematic review of noncomparative studies and case reports). It is recommended for use by the American Academy of Dermatology when standard excisional therapy is contraindicated (SOR: **C**, expert opinion).

DOI 10.1097/EBP.0000000000001792

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

In 2013, a systematic review and pooled analysis (106 noncomparative studies; 12 single case reports) assessed recurrence rates for various nonmetastatic squamous cell carcinoma (SCC) treatment modalities.[1] Studies were excluded if the review authors could not extract primary nonmetastatic SCC data or if separate data were not reported for different treatment modalities. Mean ages of the patients ranged from 63 to 75 years old in the studies which reported demographics. Follow-up periods ranged from 6 months to 7.5 years. Cryotherapy interventional

studies were limited to low-risk lesions, <2 cm in diameter. Cryotherapy demonstrated a recurrence rate of 0.8% (8 studies, N=273; 95% CI, 0.1–2, I^2=0%). For the standard excision group, lesion size varied and included lesions greater than 2 cm and higher risk characteristics (ie, depth >2 mm, metastasis, poorly differentiated) and excision margins ranged from 2 to 10 mm with a recurrence rate of 5.4% (12 studies, N=1,144; 95% CI, 2.5–9.1, I^2=81%). This analysis was limited by a lack of direct comparison between treatment modalities.

In 2018, the American Academy of Dermatology established evidence-based practice guidelines for the evaluation and treatment of cutaneous SCC based on a review the literature and expert opinion.[2] The guideline recommended that cryotherapy only be considered for low-risk lesions and when more effective therapies (microscopic or standard excision) are contraindicated or not feasible because of lack of margin control (strength of recommendation B, based on inconsistent or limited-quality patient-oriented evidence). Low-risk lesions were defined as having well-defined borders, not rapidly growing, well to moderately well differentiated, <2 mm in depth, with no perineural, vascular, or lymphatic involvement. EBP

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References

1. Lansbury L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. *BMJ*. 2013;347:f6153. [STEP 2]
2. Work Group; Invited Reviewers, Kim JYS, Kim JYS, Kozlow JH, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. *J Am Acad Dermatol.* 2018;78(3):560-578. [STEP 4]

How effective are PPIs at reducing the risk of GI bleeds in patients on anticoagulation therapy versus patients not taking PPIs?

EVIDENCE-BASED ANSWER

The effectiveness is not completely clear. Protein pump inhibitors may be associated with a decreased risk of gastrointestinal bleeds in patients on anticoagulation but the evidence is conflicting (SOR: **B**, meta-analysis and retrospective cohort).

DOI 10.1097/EBP.0000000000001787

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

A 2020 systematic review of six studies examined the effect of protein pump inhibitors (PPIs) to prevent gastrointestinal (GI) bleeds in patients who were recently started on anticoagulation.[1] Three studies were nested case–control studies or cohort studies (N=31,645) and three were retrospective cohort studies (N=123,504) for a total of 155,149 adult patients. One study was from Asia, the remaining were from Europe or the United States with an enrolled population from 40 to 84 years old. Overall, the studies demonstrated a protective effect of acid suppressants (PPIs or H2RA) against upper GI bleed in patients on dicumarinics (vitamin K antagonists; 6 trials; N=155,149, risk ratio [RR] 0.56; 95% CI, 0.38–0.83), but acid suppressants (PPIs or H2RA) had no appreciable effect on GI bleeds in patients on dabigatran (6 trials; N=155,149, hazard ratio [HR] 0.78; 95% CI, 0.44–1.4). Three studies examined upper GI bleeds, two overall GI bleeds, and one examined recurrent GI bleeds. The study based on recurrent GI bleeds was excluded from the

meta analysis. The nested case–control studies in composite showed a protective effect of PPIs (3 trials; N=6,113; RR 0.56; 95% CI, 0.52–0.83) against dicumarinic-associated upper GI bleeds on PPIs but not H2RAs (3 trials; N=6,113, RR 0.97; 95% CI, 0.52–1.8). Individually, these three studies had CIs that crossed or closely approached 1; when combined, their data became significant.

A randomized, double-blinded control trial compared the effectiveness of pantoprazole (40 mg daily) compared with placebo regarding reduction of clinically significant upper gastrointestinal events in 17,598 adult patients on anticoagulation.[2] The population studied involved patients with stable coronary artery disease or peripheral artery disease, who were at least 65 years old, or had arterial disease involving two vascular beds or two additional risk factors (not defined in study). The patients were started on rivaroxaban, rivaroxaban with aspirin, or on aspirin alone; those who were eligible were then further stratified to receive PPI or matched placebo. The primary outcome of clinically significant upper gastrointestinal events was defined as a composite of hematemesis or melena with gastroduodenal ulcer or neoplasm confirmed on endoscopy/radiography and bleeding at the time of procedure, overt gastrointestinal bleed confirmed by attending physician, occult bleeding presumed of upper gastrointestinal origin with a drop in hemoglobin of ≥2 g/dL, symptomatic ulcer with three days of gastrointestinal pain, or five lesions confirmed by endoscopy with accompanying gastrointestinal pain, obstruction, or perforation. This was over a mean follow-up period of three years (range of 2 days to 5 years and 1 month). In the pantoprazole group versus the placebo group, no significant decrease was noted in the percentage of patients with clinically significant upper gastrointestinal events (1.2% vs 1.3%, HR 0.88; 95% CI, 0.67–1.2). Post hoc analysis broadened the definition of upper GI events related to gastroduodenal ulcers and required endoscopy confirmation, removing the pain requirement. When the data were reanalyzed with these criteria, a significant reduction in bleeding gastroduodenal lesions confirmed by endoscopy/radiography was seen in the pantoprazole arm versus the placebo group (HR 0.45; 95% CI, 0.27–0.74 with a number needed to treat of 982). It should be noted that this study was paid for by Bayer, and the authors had individual grants and research funding from multiple other Pharma and Medical Tech companies.

A 2018 retrospective cohort study examined the incidence rate ratio (IRR) and risk difference (RD) per 10,000 patient-years of hospitalization for upper GI bleeds in over one million patients with oral anticoagulation who received PPI co-therapy versus no PPI co-therapy.[3] Patients newly anticoagulated with apixaban, rivaroxaban, dabigatran, and warfarin were evaluated for a total of 754,389 patient-years without PPI co-therapy and 264,447 patient-years with PPI co-therapy. A reduction was noted in both the IRR and the RD per 10,000 patients in upper GI bleed hospitalizations when PPI co-therapy was used for apixaban, dabigatran, rivaroxaban, and warfarin (**TABLE**). Overall, the study had a large patient population that was stratified based on likelihood ratios for anticoagulation-associated upper GI bleeds (lower GI bleeds and those upper GI bleeds likely not anticoagulant associated, such as mallory-weiss tears, were excluded). Patients only required one prescription fill within the last year to be included in the PPI co-therapy group. The study excluded those on multiple anticoagulants but was not able to account or evaluate for patients on concomitant low-dose aspirin or over-the-counter NSAID therapy. EBP

TABLE. Effectiveness of PPI co-therapy in preventing GI bleed hospitalizations in patients taking oral anticoagulation compared with no PPI co-therapy

Drug	IRR (95% CI)	RD per 10,000 patients (95% CI)
Apixaban	0.66 (0.52–0.85)	–24 (–38 to –11)
Dabigatran	0.49 (0.41–0.59)	–61 (–76 to –47)
Rivaroxaban	0.75 (0.68–0.84)	–36 (–49 to –22)
Warfarin	0.65 (0.62–0.69)	–39 (–44 to –34)

IRR=incident rate ratio; RD=risk difference.

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References

1. Bang CS, Joo MK, Kim B-W, et al. The role of acid suppressants in the prevention of anticoagulant-related gastrointestinal bleeding: a systematic review and meta-analysis. *Gut Liver.* 2020;14(1):57-66. [STEP 1]
2. Moayyedi P, Eikelboom JW, Bosch J, et al. Pantoprazole to prevent gastroduodenal events in patients receiving rivaroxaban and/or aspirin in a randomized, double-blind, placebo-controlled trial. *Gastroenterology.* 2019;157(2):403-412.e5. [STEP 2]
3. Ray WA, Chung CP, Murray KT, et al. Association of oral anticoagulants and proton pump inhibitor cotherapy with hospitalization for upper gastrointestinal tract bleeding. *JAMA*. 2018;320(21):2221-2230. [STEP 3]

Does COVID-19 infection provide significant postinfection immunity to COVID-19 in adults?

EVIDENCE-BASED ANSWER

Yes. Adult patients who had a previous SARS-CoV-2 (COVID-19) infection seem to have a significantly lower risk of another infection for 1–10 months compared with patients who have not been previously infected (SOR **B**: systematic review of cohort studies, 2 prospective cohort studies, surveillance study). A protective effect of 77% from reinfection is observed in patients with a history of COVID-19 infection (SOR **B**: surveillance study).

DOI 10.1097/EBP.0000000000001774

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

A 2021 systematic review of 10 longitudinal cohort studies (N=9,930,470) from six different countries (United States, Austria, Italy, Israel, England, Denmark) evaluated the risk of reinfection among individuals previously infected with COVID-19.[1] Specific demographic information for the patients was not provided; however, some of the studies used "young and healthy adults." The intervention cohorts were patients who were not previously vaccinated against COVID-19 and had experienced previous infection. Uninfected, unvaccinated patients composed the comparison cohorts. Median observation periods varied from 1 to 10.3 months. The primary outcome was testing positive for COVID-19 on a polymerase chain reaction (PCR) test during the period of observation. Patients who had initial infection experienced a 90.4% weighted average risk reduction for reinfection (10 studies, N=9,930,470; $P<.01$) compared with uninfected, unvaccinated patients. Protection against COVID-19 reinfection was seen for up to 10 months. Study limitations included requiring confirmation of infection and reinfection by PCR and review authors using studies obtained preprint and before peer review.

A 2021 prospective cohort study (n=653) evaluated the immunity to infection with COVID-19 in unvaccinated patients with and without previous infection.[2] Patients had a median age of 39 years old and were 72% female. At-risk individuals, either university healthcare workers or patients, who had a high exposure risk to COVID-19 and were reverse transcriptase PCR (RT-PCR) positive, RT-PCR negative, or without a known history of infection were included. Baseline seropositive (n=129) and seronegative (n=209) patients were verified by RT-PCR at enrollment. The remaining patients (n=315) had no positive RT-PCR test or known history of infection. The mean follow-up time was 126 days between enrollment and a follow-up at 3 to 6 months later. The primary outcome was infection with COVID-19 during the follow-up period, determined by using semiquantitative spike (S) and nucleocapsid (N) antibody titers with pseudoviral neutralization assays. Patients who became vaccinated during this time were withdrawn from the study. Significantly, fewer subsequent COVID-19 infections were observed with the initially seropositive patients compared with the seronegative cohort during the follow-up period (seropositive, 0 per 10,000 days at risk vs seronegative, 2.1 per 10,000 days at risk, $P=.0485$). Study limitations included limited data on the newer viral variants at the time of the study.

A 2021 prospective cohort study (n=209) evaluated whether antibodies or previous seropositive status to

COVID-19 was protective against reinfection during a second outbreak of COVID-19.[3] This study was not included in the 2021 systematic review study above. Patients were nursing/care home staff (n=106, no further demographics presented) and residents (n=103, median age 84 years old, about two-thirds female) from two London nursing/care homes. Previous infection was confirmed with either RT-PCR or antibody tests. The primary outcome was infection with COVID-19 during the second outbreak, determined by a positive RT-PCR test. Patients with an initial COVID-19 infection had a significantly lower incidence of infection compared with those without antibodies (1.1% vs 30.1%; relative risk [RR] 0.04; 95% CI, 0.01–0.27).

A 2022 surveillance study (n=550,168) examined the protection of prior COVID-19 infection against reinfection.[4] Patients were 20 years old and older and 56% female. Patients included in this study were identified as either having tested positive or negative for COVID-19 between March 6 and August 31, 2020. Patients who died within 90 days of their initial positive test were excluded. Patients with initial positive COVID-19 tests (n=41,647) composed the positive test group and were followed for recurrence of a positive test from 91 days after initial result through December 31, 2020. Patients with a negative test and no subsequent positive test within the study period (n=508,521) composed the test-negative comparison group. The primary outcome was either a positive COVID-19 test by PCR or antigen tests, date of death, or until December 31, 2020. Patients with no previous infection had a significantly higher risk of a positive test compared with individuals with a history of infection (1.4% vs 6.3%; RR 4.4, 95% CI, 4.1–4.8). This corresponded to a protective effect of 77.3% (95% CI, 75.4%–79.0%) from repeat infection. Study limitations included differences in risk behaviors between cohort groups, and use of antigen testing without confirmation with PCR testing. EBP

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References

1. Kojima N, Shrestha NK, Klausner JD. A systematic review of the protective effect of prior SARS-CoV-2 infection on repeat infection. *Eval Health Prof.* 2021;44(4):327-332. [STEP 2]
2. Schuler IVCF, Gherasim C, O'Shea K et al. Mild SARS-CoV-2 illness is not associated with reinfections and provides persistent spike, nucleocapsid, and virus-neutralizing antibodies. *Microbiol Spectr.* 2021;9(2):e0008721. [STEP 3]
3. Jeffery-Smith A, Iyanger N, Williams SV et al. Antibodies to SARS-CoV-2 protect against re-infection during outbreaks in care homes, September and October 2020. *Euro Surveill.* 2021;26(5):2100092. [STEP 3]
4. Spicer KB, Glick C, Cavanaugh AM, Thoroughman D. Protective immunity after natural infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) – Kentucky, USA, 2020. *Int J Infect Dis.* 2022;114:21-28. [STEP 4]

In adolescent soccer players, is the use of protective headgear more effective in preventing concussion than no headgear?

EVIDENCE-BASED ANSWER

Headgear probably does not decrease the risk of sports-related concussion in adolescent soccer players (SOR: **B**, conflicting unblinded randomized controlled trial and cross-sectional cohort study).

DOI 10.1097/EBP.0000000000001718

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

A 2019 randomized controlled trial (n=2,766) of adolescent soccer players assessed if headgear reduced the incidence of sport-related concussion (SRC).[1] High school soccer teams were recruited and randomized into headgear (n=1,505) and no headgear (n=1,545). Teams participated in the study for one or two years. Participants were interscholastic soccer players, 14 to 18 years old, and were 67% female. Athletes using headgear were allowed to pick the headgear as long as it met standards set by the National Federation of State High School

Associations. Athletic trainers reported the type of headgear worn for each practice and competition and also diagnosed and recorded SRC concussion and non-SRC injuries. Trainers and coaching staff reported the number of practices and competition athletic exposures for each participant. Overall, 130 participants suffered an SRC. No significant difference was noted in concussion rates between players wearing protective headgear verses no headgear (adjusted risk ratio 0.98; 95% CI, 0.62–1.56). No difference was noted in frequency of non-SRC injures in individuals wearing headgear versus no headgear (RR 0.91; 95% CI, 0.64-1.29). Limitations included selection bias, variation in the headgear, and inability to blind treatment groups.

A 2008 cross-sectional study (n=278) evaluated the effect of protective headgear on concussion in adolescent soccer players.[2] Male and female travel team soccer players, age 12 to 17 years old, completed a retrospective, anonymous online survey and self-reported possible concussion symptoms and whether protective headgear was worn at the time of injury. The primary outcome was number of concussions. Study authors defined a concussion as any change in cerebral function caused by a direct or indirect blow to the head, resulting in one or more acute sign or symptom: loss of consciousness, light-headedness, vertigo, cognitive or memory dysfunction, tinnitus, blurred vision, difficulty concentrating, amnesia, headache, nausea, vomiting, photophobia, or balance disturbances. No headgear use was reported by 216 participants, whereas 52 wore headgear. About half (48%) of participating athletes reported symptoms of at least one concussion. The no headgear group experienced significantly more concussions compared with the headgear group (53% vs 30% athletes reporting concussive symptoms; RR 2.65; 95% CI, 1.23–3.12). Limitations of the study include lack of randomization and the retrospective and self-reporting of the data. EBP

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References

1. McGuine T, Post E, Pfaller AY, et al. Does soccer headgear reduce the incidence of sport-related concussion? A cluster, randomised controlled trial of adolescent athletes. *Br J Sports Med*. 2020;54(7):408-413. [STEP 2]
2. Delaney JS, Al-Kashmiri A, Drummond R, Correa JA. The effect of protective headgear on head injuries and concussions in adolescent football (soccer) players. *Br J Sports Med*. 2008;42(2):110-115. [STEP 3]

Do structured exercise programs help improve back pain in helicopter pilots?

EVIDENCE-BASED ANSWER

Probably. Pilots who participate in a structured exercise program have mild improvements in muscle contractility, pain, function, and health-related quality of life compared with those who participate in a traditional exercise program (SOR: **C**, small cohort study). Participating in a structured exercise program may decrease the percentage of pilots taking sick days by up to 75% (SOR: **B**, retrospective cohort study); however, it may not have an effect on the long-term presence of transient low back pain.

DOI 10.1097/EBP.0000000000001696

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

A 2017 prospective cohort study (n=39) evaluated the effect of structured exercise programs on transient low back pain (LBP) in commercial helicopter pilots.[1] The study included 35 men and four women, all of whom self-reported LBP on at least one of three flights in the month before enrollment. Pilots were placed into two exercise groups with an intervention period of 135 days. The group A intervention (n=10) consisted of 10 exercises performed in three sets of 10 repetitions (considered "traditional exercises"). The group B intervention (n=29) consisted of four exercises (involving

TABLE. Changes in clinical measures in pilots with transient LBP completing structured exercise programs[a]

Clinical measure (range)	All pilots (n=39 Mean difference (95% CI)	Completed protocol (n=20) Mean difference (95% CI)	Group A (n=7) Mean Difference (95% CI)	Group B (n=13) Mean Difference (95% CI)
Visual analog scale (0–10)	**−1.2 (−2.0 to −0.4)**	−1.3 (−2.6 to 0.1)	0.4 (−1.0 to 1.8)	**−2.2 (−4.0 to −0.3)**
Oswestry Disability Index (0-100)	**−3.3 (−5.0 to −1.6)**	**−2.4 (−4.2 to −0.6)**	−2.3 (−6.6 to 2.0)	**−2.5 (−4.5 to −0.4)**
Euroqol-5D (0-100)	**7.4 (2.9 to 11.9)**	**12.5 (5.9 to 19.1)**	10.4 (−5.0 to 25.9)	**14 (5.7 to 22)**
Endurance (sec)	**89.6 (59.5 to 119.8)**	**99.6 (46.8 to 152.5)**	**156 (76.5 to 236.3)**	69 (−1.4 to 139.4)

[a]Statistically significant differences in bold.

concentric, isometric, and eccentric phases) using equipment and performed in a "reversed pyramid" protocol. Seven of the 10 pilots in group A and 13 of 29 pilots in group B performed the exercises per protocol. The primary outcome was increase in muscular endurance (extension, flexion, right side bridge, and left side bridge) as measured by an increase in time holding each of these positions. Secondary outcomes included the improvement in L4–L5 and L5–S1 lumbar multifidus muscle isometric contraction as measured by increase in percentage of muscle seen on ultrasound scanning, and the intensity of LBP via a 1 to 10 visual analog scale (10 = severe pain). Along with the above outcomes, the changes in quality-of-life and disability via the Euroqol-5D questionnaire and Oswestry Disability Index, respectively, were measured at baseline and after the intervention period. All pilots, regardless of the exercise group, had improvements in muscular endurance and an increase in contractility of lumbar multifidus musculature. Group B experienced an improvement in pain, function, and health-related quality of life, whereas group A had greater muscle endurance (**TABLE**). Limitations included using a nonrandomized nonblinded study design and a significant dropout rate.

A 2018 follow-up on the prospective study from 2017 (n=65) evaluated the long-term effects of exercise programs on LBP.[2] The study included the same population (n=37, 2 pilots lost to follow-up) and inclusion and exclusion criteria listed above. In addition, 28 pilots who did not participate in the structured exercise programs were included for comparison. The patients performed the same exercise programs as above, with follow-up occurring at a mean of 26 months after completing the programs. The pilots were encouraged to continue the exercise programs after the initial study period. The primary outcome was the proportion of pilots experiencing transient LBP using the same scales discussed above. The secondary outcome was the percentage of pilots taking sick days before, during, and after the exercise programs. Within the comparison group, 46% had persistent transient LBP compared with 26% of pilots in group B and 70% of pilots in group A. The percentage of pilots taking sick leave during and after intervention was unchanged within group A, whereas 26% fewer pilots took sick leave in group B (30% vs 4%, $P=.039$). Limitations of this study are similar to those from the 2017 study, including the lack of a formal randomized control design. EBP

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

References

1. Andersen K, Baardsen R, Dalen I, Larsen JP. Impact of exercise programs among helicopter pilots with transient LBP. *BMC Musculoskelet Disord*. 2017;18(1):269. [STEP 3]
2. Andersen K, Baardsen R, Dalen I, Larsen JP. Long-term effects of exercise programs among helicopter pilots with flying related LBP. *J Back Musculoskelet Rehabil*. 2018; 31(1):1-13. [STEP 3]

On physical examination, what are the best clinical findings to diagnose hip osteoarthritis?

EVIDENCE-BASED ANSWER

The best clinical examination findings to diagnose hip osteoarthritis (OA) are posterior hip pain with squatting, groin pain on abduction or adduction, weakness with abduction, and decreased hip adduction and internal rotation (SOR: **B**, systematic review of prospective cohort studies and a case–control study). Restricted and painful hip internal rotation strongly differentiates hip OA from lumbar spinal stenosis (SOR: **B**, cohort study).

DOI 10.1097/EBP.0000000000001823

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

A 2019 systematic review of five prospective cohort studies and one case–control study (N=1,324) evaluated signs and symptoms most associated with hip osteoarthritis (OA).[1] Patients who presented to a hospital or a primary care setting with atraumatic hip or groin pain and subsequently received a clinician-led physical examination with plain radiograph evaluation were included. Individuals with traumatic hip injuries or nonradiographic diagnostic evaluations were excluded. In total, 1,324 hips were evaluated, with 509 (38%) displaying radiographic evidence of OA. Comparisons were made between different physical examination findings and the likelihood of a patient having abnormalities of the hip on plain radiographs suggestive of OA. Results were reported in both positive likelihood ratios (LR+), which help rule in the diagnosis of OA, and negative likelihood ratios (LR–), which help rule out the diagnosis. After pooling data from all included studies, the physical examination findings most useful for ruling in a diagnosis of hip OA were posterior hip pain caused by squatting (LR+ 6.1; 95% CI, 1.3–29), groin pain on hip abduction or adduction (LR+ 5.7; 95% CI, 1.6–20), and abductor weakness (LR+ 4.5; 95% CI, 2.4–8.4) as measured by a goniometer or compared with the contralateral leg. The presence of normal hip passive adduction (LR– 0.25; 95% CI, 0.11–0.54) or abduction (LR– 0.26; 95% CI, 0.09–0.77) was most useful for ruling out OA in patients with hip pain. The main limitation was results from a hospital outpatient setting that may not be generalizable to individuals presenting to their primary care provider.

A 2019 prospective cohort study (n=156) compared physical examination findings for diagnosing and differentiating hip OA and lumbar spinal stenosis (LSS) to their clinical utility.[2] Patients were sampled from two spine surgery practices, two joint arthroplasty practices, and one hospital-based spine center. Those who had primary symptoms of proximal leg pain with or without buttock, hip or distal leg pain, and who had imaging-confirmed hip OA (n=77) or LSS (n=79) were included. Patients with leg pain not induced by walking and relieved with sitting and painless presentations of hip OA (restricted range of motion only) and LSS (neurological symptoms only) were excluded. For each patient, the enrolling physicians completed questionnaires that included 13 physical examination items. Affected hip range of motion examinations were compared with the asymptomatic hip. Finally, recruiting physicians offered their final diagnosis by selecting one of the following: (1) hip OA; (2) LSS; (3) concurrent symptomatic hip OA and LSS; (4) unsure; or (5) other conditions. Positive likelihood ratios were calculated for each items' ability to differentiate hip OA from LSS. Of the physical examination items, 7 of the 13 strongly favored hip OA over LSS. Restricted and painful hip flexion (LR+ 99) and hip external rotation (LR+ 99) strongly differentiated hip OA from LSS. Restricted and painful flexion, adduction, and internal rotation testing (LR+ 33), hip internal rotation (LR+ 24), flexion abduction external rotation testing (LR+ 21), shifting weight away from painful leg when standing (LR+ 10), and walking with a limp (LR+ 9), while diagnostic of hip OA, only moderately differentiated hip OA from LSS. The CIs were not available in the study. Harms included pain symptoms induced during physical examinations. Limitations included the assumption that patients were correctly diagnosed by the enrolling physician because their clinical opinion was the standard for calculations of sensitivities and LR+, respectively. EBP

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References

1. Metcalfe D, Perry DC, Claireaux HA, Simel DL, Zogg CK, Costa ML. Does this patient have hip osteoarthritis?: the rational clinical examination systematic review. *JAMA*. 2019; 322(23):2323-2333. [STEP 3]
2. Rainville J, Bono JV, Laxer EB, et al. Comparison of the history and physical examination for hip osteoarthritis and lumbar spinal stenosis. *Spine J.* 2019; 19(6):1009–1018. [STEP 3].

For term singleton pregnancies during second stage of labor, is ultrasound a useful tool to predict need for an operative delivery?

EVIDENCE-BASED ANSWER

The angle of progression shows promise as an ultrasound measurement and is most predictive of spontaneous vaginal delivery (SVD) if over 140° (SOR: **B**, systematic review of randomized controlled trials [RCTs]). Correction of ultrasound-identified malpresentation may lead up to 30% fewer operative deliveries (SOR: **B**, single RCT). Additional ultrasound measurements which may prove to be predictive of successful SVD included a narrower midline angle (30°±15°) and a shorter head-symphysis distance (13 mm±4.6 mm) (SOR: **C**, prospective cohort study).

DOI 10.1097/EBP.0000000000001796

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

A 2021 systematic review and meta-analysis of eight RCTs (N=877 pregnancies) evaluated the ability of angle of progression (AOP) measurement to predict spontaneous vaginal delivery (SVD) versus operative delivery (OD: cesarian section and instrumental vaginal delivery).[1] The trials included uncomplicated singleton pregnancies >37 weeks gestation with cephalic presentation; two trials limited their population to nulliparous women. All patients had transperineal ultrasound (TPUS) measuring AOP performed at the beginning of the second stage of labor before pushing. Patients presenting with a noncephalic presentation, multiple gestation, or severe maternal or fetal complications affecting labor were excluded. AOP was obtained through TPUS and defined as the measured angle between the lower edge of the pubic symphysis and the tangent line to the leading fetal skull edge. The primary outcome of the pooled sensitivity and specificity of AOP in predicting SVD was 80% (95% CI, 71–86%) and 81% (95% CI, 72–88%), respectively. Subgroup analysis further categorized AOP into subgroups: 108–119°, 120–140°, and 141–153°. The <120° subgroup had the highest sensitivity, 94% (95% CI, 88–97%), and the >140° subgroup had the highest specificity of 82% (95% CI, 66–92%). Strengths of the review included the prospective design of the RCTs and the standardized measurement and timing of measurement of AOP. Limitations included the small number of studies and failure to adjust results for fetal head position and parity.

A 2021 multicenter, prospective RCT (n=257 singleton term pregnancies) evaluated the ability of an ultrasound evaluating fetal presentation to predict method of delivery.[2] The trial included women (mean age 30 years old, 90% nulliparous, mean gestational age 40 weeks, and mean body mass index 28 kg/m^2) in early second stage of labor who had epidural anesthesia with ultrasound-confirmed occiput posterior or occiput transverse position. Based on the ultrasound results, patients either received prophylactic manual rotation of the fetus to the occiput anterior position (OA) in the early second stage of labor (n=126) or had expectant management (n=131). Ultrasound was again performed to confirm fetal position postmaneuver. The primary outcome of the study was need for OD. Secondary outcomes included length of second stage of labor, postpartum hemorrhage (>500 mL of blood loss), blood transfusion, maternal intensive care unit [ICU] admission, operative complications after cesarean delivery,

episiotomy, perineal tears, anal sphincter injuries, neonatal trauma, and neonatal ICU admissions. Manual rotation performed after initial confirmatory ultrasound was successful in 90% of patients with 76% resulting in SVD. Intention-to-treat analysis revealed a decrease in OD in the intervention group compared with control (29% vs 41%; 95% CI, −15.7 to −7.9) and a significantly shorter length of time for second stage of labor for the intervention group (147 min vs 164 min; $P=.028$). No statistical difference was observed in any of the other secondary outcomes. A key limitation was the inability to blind providers to the intervention.

A 2019 observational, prospective cohort study (n=109) explored the ability of intrapartum ultrasound to predict the likelihood of SVD during a prolonged second stage of labor.[3] The trial included nulliparous women (mean age 33 years old) with singleton pregnancies at an average 40 weeks' gestational age who had a prolonged second stage of labor (defined as active pushing for >120 min). All women received both transabdominal ultrasound (TAUS) to determine fetal head position and TPUS to measure the AOP. The primary outcome of this study was to compare TAUS and TPUS findings among women who had SVD versus those who required OD. Of the 109 women, 40 (37%) delivered through SVD, 40 (37%) delivered through vacuum-assisted delivery, and 29 (27%) underwent cesarean delivery. SVD occurred in 90% of women with fetus in OA versus only 53.2% who were not in the OA position ($P<.0001$). Sonographic measurements included the transperineal midline angle (angle between fetal cerebral interhemispheric echogenic line and anteroposterior axis of the pelvis) and the head-symphysis distance (sagittal distance from fetal skull to lower edge of pubic symphysis). A narrower transperineal midline angle (30° vs 54°; $P<.001$; sensitivity 82%; 95% CI, 0.6–0.95; specificity 75%; 95% CI, 0.6–0.87) and shorter head-symphysis distance (13 mm vs 20 mm; $P<.001$; sensitivity 80%; 95% CI, 0.64–0.91; specificity 63%; 95% CI, 0.51–0.75) were found to be independently significant predictors of SVD. Limitations included low generalizability because the study was performed in two Italian medical centers. This study was also limited to nulliparous women and lacked sufficient power to assess for statistically significant differences in maternal and perinatal outcomes. EBP

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

References

1. Nassr AA, Berghella V, Hessami K, et al. Intrapartum ultrasound measurement of angle of progression at the onset of the second stage of labor for prediction of spontaneous vaginal delivery in term singleton pregnancies: a systematic review and meta-analysis. *Am J Obstet Gynecol.* 2022;226(2):205-214.e2. [STEP 1]
2. Blanc J, Castel P, Mauviel F, et al. Prophylactic manual rotation of occiput posterior and transverse positions to decrease operative delivery: the PROPOP randomized clinical trial. *Am J Obstet Gynecol.* 2021;225(4):444.e1-444.e8. [STEP 2]
3. Dall'Asta A, Angeli L, Masturzo B, et al. Prediction of spontaneous vaginal delivery in nulliparous women with a prolonged second stage of labor: the value of intrapartum ultrasound. *Am J Obstet Gynecol.* 2019;221(6):642.e1-642.e13. [STEP 3]

Is combination nicotine replacement therapy more effective than single nicotine replacement therapy for smoking cessation?

EVIDENCE-BASED ANSWER

Probably. Combination nicotine replacement therapy (NRT) using both a nicotine patch and a fast-acting form (such as gum, lozenge, or inhaler) results in a 15% to –36% higher quit rate at 6 to 12 month follow-up compared with single-form NRT with an NNT of 29 (SOR: **A**, meta-analysis of randomized controlled trials [RCTs] and subsequent RCT with some conflicting outcomes).

DOI 10.1097/EBP.0000000000001794

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

A 2019 meta-analysis of 64 RCTs (N=41,509) examined the effectiveness and safety of different doses, deliveries, and durations of nicotine replacement therapy (NRT).[1] Patients were adults with a mean age of 45 years old, recruited from community and various clinical settings in Australia, Europe, and Asia. Further patient demographics were not presented. A subgroup analysis (14 RCTs, N=11,356) was conducted to compare combination NRT (n=5,218) versus single-form NRT (n=6,138) and its effect on smoking cessation. The trials included smokers of any age, who smoked at least 15 cigarettes a day with any level of previous nicotine dependence and were motivated to quit. The combination NRT groups were treated with a nicotine patch and a fast-acting form (eg, gum, lozenges, nasal spray, or inhaler) whereas the single NRT groups received any one type of NRT. The primary outcome was smoking cessation assessed through a mixture of self-reported abstinence of at least 6 months and expired carbon monoxide levels of less than or equal to 10 ppm. Patients were followed for 6 to 12 months. Combination NRT resulted in significantly higher quit rates at 6 to 12 months than single-form NRT (14 RCTs, N=11,356; 17.4% vs 13.9%; risk ratio [RR] 1.25; 95% CI, 1.15–1.36; I^2=3.57%; NNT=29). Combination NRT was significantly more effective than patch alone (12 RCTs, N=8,992; 16.0% vs 13.3%; RR 1.23; 95% CI, 1.12–1.36; I^2=32%; NNT=36) and significantly more effective than fast-acting form of NRT alone (6 RCTs, N=2,364; 20.8% vs 15.9%, RR 1.30; 95% CI, 1.09–1.54; I^2=0%; NNT=20). These results were clinically meaningful. No evidence of an effect on cardiac adverse events, serious adverse events, or withdrawals were reported. However, these were measured variably and infrequently across trials, resulting in low or very low certainty evidence for all adverse events comparisons. A notable study limitation was that six of the 14 RCTs were at high risk of blinding bias in either the performance or detection domains.

A 2019 RCT (n=560; published after the search date of the above review) assessed smoking abstinence rates in patients using combination NRT compared with single-form NRT.[2] Patients were recruited from 20 primary care clinics in Hong Kong and were 85% male with a mean age of 50 years old who smoked an average of 18 cigarettes a day. Exclusion criteria included smokers with unstable angina, severe cardiac arrhythmia, recent acute myocardial infarction or cerebrovascular accident in the last 3 months, smokers pregnant or breast-feeding, unable to use gum, or those with a history of failure with NRT. The intervention group (n=274) received a combination of nicotine patch and nicotine gum for 8 weeks while the comparison group (n=286) received nicotine patch alone for 8 weeks. The primary outcome was smoking abstinence at 52 weeks. Secondary outcomes included smoking abstinence at 4, 12, and 26 weeks, assessed by self-report of 7-day point prevalence abstinence validated with exhaled carbon monoxide levels. At 4 weeks, the combined NRT group had significantly higher abstinence rates than the single NRT group (35.8% vs 28%; odds ratio 1.4; 95% CI, 1.0–2.1; NNT=13). However, no significant differences were observed in smoking abstinence rates between the combined group and single NRT group at 12 weeks (22% vs 17%), 26 weeks (17% vs 11%), and 52 weeks (20% vs 14%). Overall, 3.4% of smokers developed side effects, including itch, rash, and palpitations after using NRT, with no significant difference in the side effects between the two groups. This study was limited by a lack of blinding and a high attrition rate. EBP

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References

1. Lindson N, Chepkin SC, Ye W, et al. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2019;(4):CD013308. [STEP 1]
2. Leung MKW, Bai D, Yip BHK, et al. Combined nicotine patch with gum versus nicotine patch alone in smoking cessation in Hong Kong primary care clinics: a randomised controlled trial. *BMC Public Health*. 2019;19(1):1302. [STEP 2]