November 2023
Volume 26 | Number 11

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

November 2023
Volume 26 | Number 11

EVIDENCE-BASED PRACTICE
Volume 26 | Number 11

FPIN
Family Physicians Inquiries Network

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

TABLE OF CONTENTS

VOL 26 | NO. 11 | November 2023

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

EDITORIAL

DIVING FOR PURLs

IN DEPTH

GEMS

HELPDESK ANSWERS

SPOTLIGHT ON PHARMACY

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

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

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

STATEMENT OF PURPOSE

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

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.

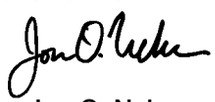
Null field research

I love the clear night sky and consider a galaxy of stars overwhelmingly beautiful. I know the names of some brighter stars and can find a couple of the more famous constellations: Orion's Belt, the Big Dipper, the Pleiades. But several years ago, during a trip to South America, the night sky was suddenly baffling. Without a sky map, I couldn't even find the fabled Southern Cross—there were crosses *everywhere* up there. It brought home the concept that patterns we see in random fields are projections, not reality.

Some investigators in research methods decided to test what evidence-based medicine might project into a random, meaningless data set.[1] To do so, they identified a field of research they were certain contained no real effects—homeopathy, where treatments consist of solutions so dilute, they cannot be reasonably expected to have biological action. The technical term the researchers used was a "null field."

Next, they collected 50 RCTs of homeopathic therapies from 13 highly cited meta-analyses and looked to see how big an effect size our familiar and trusted research system had created (likely out of thin air). It turned out that 80% of the studies found a positive effect favoring homeopathy over placebo. The few studies that favored placebo did not report their results correctly because of math and protocol flaws. When all the studies were summed together (and their math corrected), homeopathy still appeared to demonstrate a small to moderate positive effective size (Hedges' g 0.36; 95% CI, 0.21–0.51), which corresponded to an odds ratio of 1.94.

The authors concluded that null field research would be a helpful corrective to overreaching results in the rest of medical research. I don't have enough statistical training to know how this might work, but I certainly agree in principal. Humans are only too willing to see patterns in random dots (I'm looking at you Orion) and much pseudoscience is kept alive by the tendency. Until the details are worked out, maybe I'll just take 0.36 off any reported effect size and sagely contemplate the remainder.



Jon O. Neher

DOI 10.1097/EBP.0000000000002047

Reference

1. Sigurdson MK, Sainani KL, Ioannidis JPA. Homeopathy can offer empirical insights on treatment effects in a null field. *J Clin Epidemiol*. 2023; 155:64–72.

The role of pre/probiotics in the treatment of bacterial vaginosis

Afifirad R, Darb Emamie A, Golmoradi Zadeh R, Asadollahi P, Ghanavati R, Darbandi A. Effects of Pro/Prebiotics Alone over Pro/Prebiotics Combined with Conventional Antibiotic Therapy to Treat Bacterial Vaginosis: A Systematic Review. *Int J Clin Pract*. 2022; 2022:4774783. doi:10.1155/2022/4774783

DOI 10.1097/EBP.0000000000001911

This 2022 systematic review of 24 mostly randomized controlled trials (RCTs) examined the efficacy of probiotics or prebiotics (with or without antibiotics) for the treatment of bacterial vaginosis in 4,146 pregnant and nonpregnant women. Study participants' mean age was 32 years (range, 18–35 years). Seven trials (N=1,898) were in pregnant women. Sixteen different pro/prebiotic species were administered orally or vaginally and were compared with various placebos or other controls. Duration of therapy was broad, ranging from four days to 42 weeks. Most trials focused on disease-oriented outcomes such as changes in vaginal swab characteristics or microscopic analysis (Amsel criteria or Nugent score). One RCT (N=644) evaluated correlation of oral probiotic versus placebo and rates of preterm birth, yet the systematic review contradicts itself between a table and the text whether there was any benefit. One other RCT in pregnant patients (N=400) followed them through pregnancy and then breastfeeding their infants and reportedly assessed for postpartum anxiety and depression as well as infant eczema, but results were only reported for improved vaginal microbiota. Four other RCTs (N=571) reportedly evaluated patient-oriented outcomes such as "improved symptoms," yet researchers did not elaborate further on this and simultaneously stated disease-oriented outcomes such as "improved colonization" or "improved BV recovery rate." All-in-all, the reporting of patient-oriented outcomes was lacking.

Due to significant heterogeneity between the trials, a meta-analysis could not be performed. No adverse events were noted, although it was unclear how well this was studied or reported. A disparity was noted between the reported number of trial participants in the text and the first table of the review (N=8,242) and a second table listing all individual studies with respective number of patients (N=4,146). There was no clear explanation for this difference in the review itself or a supplemental online table.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching PubMed, UptoDate, and DynaMed with the terms "probiotics," prebiotics," and "bacterial vaginosis" 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: Pro/prebiotics appear safe and are generally inexpensive, but there is insufficient valid evidence of effectiveness in this review to support their use in treating bacterial vaginosis.

Leah Soley, MD
Amanda Peterson, DO
Timothy Mott, MD
Foley Hospital Corporation/South Baldwin Regional Medical Center, Foley, AL

The corresponding author is Timothy Mott, MD; tfmott@yahoo.com.

The authors declare no conflict of interest.

Increased risk for breast cancer with synthetic progestin HRT for menopausal symptoms

Citation: Abenhaim HA, Suissa S, Azoulay L, Spence AR, Czuzoj-Shulman N, Tulandi T. Menopausal Hormone Therapy Formulation and Breast Cancer Risk. *Obstet Gynecol*. 2022;139(6):1103-1110. doi:10.1097/AOG.0000000000004723

DOI 10.1097/EBP.0000000000001897

This 2022, nested, case–control study evaluated whether the increased risk of breast cancer in menopausal women on hormone replacement therapy (HRT) is

dependent on the formulation of estrogen and progesterone used. Women registered in the UK Clinical Practice Research Datalink between January 1, 1995 and December 31, 2014 were included for analysis. Researchers excluded women who were <50 years old, entered the database after 2014, or had less than one year in the cohort. From this population (n=561,379), 43,183 cases of breast cancer were identified using a record audit algorithm and 1:10 age-matched with controls. Both groups were similar in age and duration of follow-up. The cases were more likely to have higher BMI, reported smoking, alcohol consumption, endometrial cancer, hysterectomy, oophorectomy, family history of breast cancer, and reported use of oral contraception. The adjusted odds ratio (aOR) for breast cancer increased with any HRT (aOR 1.12; 95% CI, 1.09–1.15) or synthetic progestogens (aOR 1.28; 95% CI, 1.22–1.35), whereas no statistically significant elevated risk was noted with bioidentical estrogens (aOR 1.04; 95% CI, 1.00–1.09), animal-derived estrogen (aOR 1.01; 95% CI, 0.96–1.06), or bioidentical progestogens (aOR 1.04; 95% CI, 1.00–1.09). To identify closer association between HRT alone and breast cancer, the case–control groups were age restricted to 50 to 60 year olds and OR associations were unchanged. The study was limited by discordance between the cases and controls in regards to risk factors for breast cancer, such as higher BMI, family history of breast cancer, and oral contraception use. The study did not statistically assess these risk factors, therefore confounding the validity of the study.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching PubMed with the terms ["postmenopausal" and "hormone replacement therapy," and "breast cancer"] to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: Women treated for menopausal symptoms with HRT in the total cohort had an increased risk of breast cancer. There seems to be a stronger association with synthetic progestogens (predominantly medroxyprogesterone acetate). Common confounding factors include higher BMI, tobacco and alcohol use, and family history of breast cancer. There should be shared decision making that acknowledges all risk factors present and considers hormone type when prescribing.

Ariel Hoffman, MD
Robert Powell, DO
Tyler R. Reese, MD

Madigan Family Residency Program, JBLM, WA
The corresponding faculty author on the manuscript is Tyler R Reese; Tyler.R.Reese2.mil@health.mil
The authors declare no conflicts of interest.

Computerized cognitive behavior therapy for depression

Wright JH, Owen J, Eells TD, et al. Effect of Computer-Assisted Cognitive Behavior Therapy versus Usual Care on Depression Among Adults in Primary Care: A Randomized Clinical Trial. JAMA Network Open. 2022;5(2):e2146716. doi:10.1001/jamanetworkopen.2021.46716

DOI 10.1097/EBP.0000000000001769

This randomized clinical trial was designed to evaluate whether a 12-week clinician-supported computer-assisted cognitive behavioral therapy (CCBT), in addition to treatment as usual (TAU), reduced symptoms of depression to a greater degree than TAU alone in primary care patients with depression. The "Good Days Ahead" computer program was used for the CCBT intervention. The "clinician support" for the CCBT group included weekly phone calls with a mental health professional. The study was funded by the Agency for Healthcare Research and Quality (AHRQ).

A sample of 175 patients (mean age 47 years old) from multiple primary care clinic sites in Kentucky was predominately female (85%) and had a high proportion of individuals who identified as racial and ethnic minority groups: 27% African American, 8.6% multiracial, 2.5% Hispanic, and 1.2% American Indian or Alaska Native. Annual income of less than $30,000 was reported by 88 of 143 patients (62%). Other baseline demographics were quite similar between groups. Baseline PHQ-9 scores ranged from 15 to

18 indicating moderately severe depression. Overall, 95 patients (54%) were randomly assigned to clinician-supported CCBT and 80 (46%) to TAU. Dropout rates were 22% for CCBT (21 patients) and 30% for TAU (24 patients).

The primary study was the change in PHQ-9 between baseline and end of the 12-week trial, with additional three and six months of follow-up. Using an intention-to-treat analysis, greater improvement was seen in the CCBT group than the TAU group: posttreatment mean difference [MD] −2.5 (95% CI, −4.5 to−0.9); three-month follow-up MD −2.3 (95% CI, −4.5 to−0.8); and at six-month follow-up MD −3.2 (95% CI, −4.5 to−0.76).

However, the authors noted that, for moderately severe depression, the minimally clinically important difference (MCID) in the PHQ-0 for the effective dose-25 (the level where 25% of patients respond) is a reduction of 1 to 3 points. The effective dose-50 (where 50% of patients respond) is a reduction of 5 to 7 points.[1]

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 term "computerized CBT" 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: Clinician-supported CCBT, in addition to TAU, demonstrated statistically improved PHQ-9 treatment scores compared with TAU alone. However, fewer than half of patients would see a significant improvement with this addition to usual care.

Marjorie Scaffa, PhD, LPC
Michael Marfice, MD
Alan Reagan, MD
South Baldwin Regional Medical Center Family Medicine Residency, Foley, AL

The corresponding author is Timothy Mott, MD; tfmott@yahoo.com.
The authors declare no conflicts of interest.

Reference

1. Bauer-Staeb C, Kounali DZ, Welton NJ, et al. Effective dose 50 method as the minimal clinically important difference: evidence from depression trials. *J Clin Epidemiol.*, 2021;137:200-208. [STEP 2]

What's the best medication for diabetic peripheral neuropathy? That one

Tesfaye S, Sloan G, Petrie J, et al. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial [published correction appears in *Lancet*. 2022 Sep 10; 400(10355):810]. *Lancet*. 2022; 400(10353):680-690. doi:10.1016/S0140-6736(2201472-6

DOI 10.1097/EBP.0000000000001914

This was a multicenter, randomized, double-blinded, crossover trial evaluating the effectiveness of multiple medications in patients with diabetic peripheral neuropathic pain. Included patients had a baseline of at least four out of 10 on the pain numerical rating scale (NRS), and the study compared these with NRS scores following six weeks of monotherapy and later compared these again with NRS scores following 10 more weeks of a sequential addition of a second agent among those patients with persistently suboptimal pain relief at the end of the monotherapy period (defined as NRS score>3). The medications examined were amitriptyline, duloxetine, and pregabalin. (Gabapentin was omitted from the study protocol given its similarity to pregabalin and its more complex 3-times-daily dosing.) Whether a second agent was sequentially added, each patient received a second pill nevertheless, which either contained an actual medication or placebo. Each patient had the opportunity to participate in all three medication-combination pathways, with a two-week medication washout period between pathway transitions. Most patients rotated through all three treatment pathways. Among all treatment pathways, no other analgesics were used aside from paracetamol. Patients were largely similar among study arms, although not necessarily representative of the general population, with an average age of 61 years, 74% male, 94% white, average A1c 8% to 9%, average BMI 31.7 kg/m^2, had an average duration of

diabetes of 15.1 years, an average of 4.9 years of neuropathic pain, and average baseline NRS score of 6.6. Patients with an an HbA1c of >12% or GFR of <30 mL/min/1.73 m^2 were excluded from the trial. The primary endpoint evaluated was the difference in seven-day average daily NRS scores measured at the end of each 16-week treatment pathway. All medication groups combined, the mean NRS score decreased from a mean of 6.6 at baseline to 3.3 (no *P* value provided), with no significant difference when comparing total NRS score reduction among these pathways. Mean NRS reduction in patients on combination therapy from week 6 to week 16 (inadequate response to monotherapy and progressed to combination therapy) was significant (MD 1.0; 98.3% CI, 0.6–1.3), whereas the change in patients that remained on monotherapy from week 6 to 16 was not significant (MD 0.2; 98.3% CI, -0.1–0.5). Secondary endpoints included quality of life, proportion of patients achieving 30% and 50% pain reduction from baseline, insomnia severity index scores, and patient's preferred treatment pathway at the trial's conclusion, but results were not clearly presented.

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	No	Clinically meaningful	Yes

Bottom line: This trial shows us that there is no superior single medication nor combination of medications for the treatment of diabetic peripheral neuropathic pain. The results redemonstrated that monotherapy is clearly better than no therapy, and no combination of medications are better than any other combination, which is consistent with current practice guidelines. Providers can feel confident in their choice of first-line agent, as well as in their choice of an additional agent, while taking side effect profile and comorbidities into consideration for each patient.

Cristina Rabazza, MD
Corey Lyon, DO
University of Colorado Family Medicine Residnecy, Denver, CO

The Corresponding Faculty Author on the manuscript is: Corey Lyon; corey.lyon@cuanschutz.edu

The authors declare no conflict of interest.

Acupuncture for postpartum pain

Citation: Usichenko TI, Henkel BJ, Klausenitz C, et al. Effectiveness of Acupuncture for Pain Control After Cesarean Delivery: A Randomized Clinical Trial [published correction appears in JAMA Netw Open. 2022 Apr 1; 5(4):e229622]. *JAMA Netw Open*. 2022; 5(2):e220517. https://doi:10.1001/jamanetworkopen.2022.0517

DOI 10.1097/EBP.0000000000001855

In Germany from January 2015 to June 2018, acupuncture was compared with sham therapy for postpartum pain control in women 19 to 45 years old undergoing elective cesarean section under spinal anesthesia. Women were included if they had no opioid or psychotropic medicine history and excluded if they had alcoholism, a history of psychiatric disease, skin infections at acupuncture sites, surgeries lasting greater than an hour, a need to switch to general anesthesia, or intraoperative complications. Two randomized, controlled study arms of 60 women each received standard pain therapy in addition to indwelling intradermal needle acupuncture or nonpenetrating intradermal needles. In addition, the sham intervention was placed with simultaneous utilization of a thin-tipped neural pen to simulate the feeling of acupuncture needle insertion. Both interventions were placed before the administration of spinal anesthesia and remained in place for three days' postpartum. A third arm of the trial included 60 women who were recruited in a nonrandomized fashion to represent a "standard of care" comparison.

The primary outcome was pain intensity with movement, assessed on the first postoperative day, using the patient-reported and validated 11-item Verbal Rating Scale (VRS-11). Multiple patient-oriented secondary outcomes included intensity of pain on first postoperative day and day of discharge, incidence of nausea, vomiting, or tiredness, quality of life assessments related to pain, use of pain medications, and time to mobilization and removal of the Foley catheter. No dropouts were found, and less than 7% of patients had incomplete data for the intention-to-treat analysis. The trial occurred at a single tertiary care hospital with demographics

consistent across each study arm. All patients self-identified as "Non-Hispanic/White" and a mean age of 31 years old.

The primary outcome of mean pain intensity with movement on the first postoperative day was lower in the acupuncture group than both the sham group (4.7 vs 6.0 points on the VRS-11; Cohen *d* 0.73; 95% CI, 0.31–1.01) and the standard of care group (6.3 points; Cohen *d* 1.01; 95% CI, 0.63–1.4).

Among secondary outcomes, for the rate of mobilization on the day of surgery, the acupuncture group was higher than both the sham group (relative risk [RR] 2.1; 95% CI, 1.4–3.3) and the standard of care group (RR 3.6; 95% CI, 2.0–5.8). Also, on postoperative day one, Foley catheters were removed at slightly higher rates in the acupuncture group versus the sham group (RR 1.3; 95% CI, 1.1–1.6) and the standard of care group (RR 1.4; 95% CI, 1.1–1.6). The remainder of the secondary outcomes were equivalent among groups.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching PubMed with the terms "acupuncture AND postpartum pain" 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	Yes	Clinically meaningful	No

Bottom line: This study suggests safety and effectiveness for acupuncture in relieving pain and improving mobilization after elective cesarean section. Generalizability from the single-center, White German patient demographic studied is limited. Also, clinical significance is questionable with an established minimal clinically important difference of two points for the verbal pain scale used and the reported difference in mean pain intensity for the primary outcomes proving less than two points.

Timothy Mott, MD
Paris Christodoulides, MD
Brenda Nguyen, DO
South Baldwin Regional Medical Center Family Medicine Residency, Foley, AL

The corresponding faculty author on the manuscript is Timothy Mott; tfmott@yahoo.com.
The authors declare no conflict of interest.

In postpartum women, does any form of immediate postpartum contraception decrease pregnancy rates at 1 year compared to delayed postpartum contraception?

EVIDENCE-BASED ANSWER

It is unclear. No difference is observed in pregnancy rates at 12 months in patients receiving a contraceptive implant immediately before postpartum discharge versus standard timing (SOR: **B**, single randomized controlled trial). The relative risk of pregnancy by 12 months is five times higher in adolescents who do not choose a postpartum implant before hospital discharge compared with patients who do (SOR: **B**, prospective cohort study). Repeat pregnancies at 18 months may be less likely when using immediate postpartum long-acting contraception and more likely with progestin-only pills (SOR: **B,** retrospective cohort study).

DOI 10.1097/EBP.0000000000001827

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

A 2017 nonblinded randomized controlled trial (n=96) evaluated the efficacy of an etonogestrel-releasing contraceptive implant, comparing immediate versus delayed postpartum placement.[1] Patients were on average 21 years old, and 14% were nulliparous. Patients were described as African American (27%), Hispanic/Latina (40%), and White (30%). All delivered at an academic tertiary care hospital in North Carolina. Researchers inserted the contraceptive implant during the postpartum hospital stay for patients in the intervention group (immediate insertion). Patients in the control group received an implant at a routine six weeks postpartum visit (delayed insertion). The primary outcome was contraceptive implant use at one year after delivery, and a secondary outcome was pregnancy rate during the 12-month follow-up period. Implant continuation rates at one year were similar between the immediate and delayed insertion groups (81% vs 78%, respectively, $P=.7$). At one year, seven women had become pregnant: five of 37 (13.5%) in the immediate insertion group and two of 27 (7%) in the delayed insertion group ($P=.4$). All pregnancies occurred in patients who never had an implant or had the implant removed. Limitations included a 33% loss to follow-up, and researchers confirmed implant placement in only 67% of patients in the delayed insertion group.

A 2012 prospective cohort study (n=396) examined the effectiveness of immediate postpartum contraceptive implants compared with other methods.[2] Patients were adolescents with a mean age of 18.6 years old; at least 68% were described as Black or Hispanic women, and 77% were primiparous. All patients delivered at a single university hospital in Colorado. The intervention group received an etonogestrel-releasing contraceptive implant before hospital discharge, and the control group chose other contraceptive methods including no contraception, condoms, progestin-only methods prescribed any time postpartum, intrauterine devices (IUDs) placed after six weeks postpartum, and etonogestrel-releasing implants or oral contraceptive pills initiated after four weeks postpartum. The primary outcome was repeat pregnancy within 12 months, which was significantly higher in the control group than the intervention group (18.6% vs 2.6%; relative risk 5.0; 95% CI, 1.9–13). Consistent contraception use, a secondary outcome defined as maintaining at least one highly effective contraceptive method 80% or more of the time between six weeks and 13.5 months after delivery, was greater in the intervention versus control group (94% vs 52%; $P<.001$). Limitations of the study included a 19% versus 10% loss to follow-up in the control versus intervention groups.

A 2019 retrospective cohort study (n=804) examined medical record data to assess the prevalence and risk factors for rapid repeat pregnancy (RRP) among a diverse urban population at a single academic medical system in Pennsylvania.[3] Patients had a mean age of 28 years old and were predominantly Black or White women with term deliveries and low parity. Patients who received no postpartum care within the health system and those receiving postpartum tubal ligation were excluded (n=59). The intervention group received a postpartum long-acting contraception (LARC; IUD or implant) before hospital discharge, and the control

group received any other form of contraception (including none) started after hospital discharge. The primary outcome of RRP (defined as pregnancy within 18 months of the index pregnancy) was adjusted for age, race, insurance, hospital, and parity. Women who had an RRP were approximately half as likely to have used an immediate postpartum LARC method at 18 months (adjusted odds ratio [aOR] 0.45; 95% CI, 0.24–0.85). Those who had an RRP were five times more likely to have been prescribed progestin-only pills (aOR 5.1; 95% CI, 2.2–12.1) when compared with any other reversible method, including no method at all. EBP

Courtney Horton, MD, MPH
Alan Gill, MD
Tacoma Family Medicine Residency Program, Tacoma, WA

The corresponding author is Alan Gill, MD; alan.gill@multicare.org

The authors declare no conflicts of interest.

References

1. Bryant AG, Bauer AE, Stuart GS, et al. Etonogestrel-releasing contraceptive implant for postpartum adolescents: a randomized controlled trial. *J Pediatr Adolesc Gynecol*. 2017;30(3):389-394. [STEP 2]
2. Tocce KM, Sheeder JL, Teal SB. Rapid repeat pregnancy in adolescents: do immediate postpartum contraceptive implants make a difference? *Am J Obstet Gynecol*. 2012; 206(6):481.e1-481.e7. [STEP 3]
3. 'Sackeim MG, Gurney EP, Koelper N, Sammel MD, Schreiber CA. Effect of contraceptive choice on rapid repeat pregnancy. *Contraception*. 2019;99(3):184-186. [STEP 3]

Can aspirin be used as thromboprophylaxis in extremity fractures?

Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture

Major Extremity Trauma Research Consortium (METRC), O'Toole RV, Stein DM, et al. Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture. *N Engl J Med*. 2023; 388(3):203-213. doi:10.1056/NEJMoa2205973
DOI 10.1097/EBP.0000000000001958

KEY TAKEAWAY: Thromboprophylaxis with aspirin is noninferior to low-molecular-weight heparin in preventing death in hospitalized patients with operative extremity fractures and any pelvic or acetabular fracture. Aspirin is also associated with low 90-day mortality and low incidence of deep vein thrombosis and pulmonary embolism.

STUDY DESIGN: multicenter, randomized, noninferiority trial

LEVEL OF EVIDENCE: Level II

BACKGROUND: The current standard of care for orthopedic trauma is to provide venous thromboembolism (VTE) prophylaxis in the hospital and after discharge. This study was created to determine the safety and effectiveness of aspirin alone as thromboprophylaxis in comparison with LMWH because aspirin is a more convenient and less expensive option.

PATIENTS: patients with an extremity fracture requiring operative care or any fracture of the pelvis or acetabulum
INTERVENTION: Aspirin
CONTROL: Low-molecular-weight heparin
OUTCOME:

Primary: death from any cause at 90 days
Secondary: nonfatal pulmonary embolisms (PE), deep vein thrombosis (DVT), and bleeding complications
METHODS BRIEF DESCRIPTION:

A total of 12,211 patients were evaluated at 21 trauma centers in the United States and Canada.

- Patients were 18 years or older (average age of 44.6)
- Inclusion criteria: operatively treated extremity fracture or any pelvic or acetabular fracture
- Exclusion criteria: hand and forefoot fractures, extremity fractures not requiring operative management, history of venous thromboembolism in the past six months, or history of chronic blood clotting disorders.
- Demographics: 62.2% male, and most of the study patients (63.2%) were non-Hispanic Whites, followed by non-Hispanic Black (20%), Hispanic (12.4%), and other (3.4%)

Patients were randomized into either:

- Intervention group: received aspirin 81 mg PO BID while hospitalized
- Comparison group: LMWH 30 mg SQ BID while hospitalized
- Patients and physicians were aware of trial group assignments, but the thromboprophylaxis agent was concealed.

Decisions for thromboprophylaxis at hospital discharge varied by institution based on institution-specific guidelines and protocols.

- Patients who qualified for thromboprophylaxis at discharge were prescribed a median of 21 days of outpatient aspirin or LMWH, depending on group assignment.

Outcomes were measured by clinical appointment or phone interview within 90 days after randomization.

INTERVENTION (# IN THE GROUP): 6101
COMPARISON (# IN THE GROUP): 6110

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary outcome:

- No significant difference was observed in death at 90 days between aspirin and LMWH (0.78% vs 0.73%, respectively; difference 0.05% points, 96.2% CI, –0.27 to 0.38).

Secondary outcomes:

- No significant difference was observed in death caused by pulmonary embolism between patients who received aspirin versus LMWH
- No significant difference was observed in the percentage of nonfatal emboli in patients who received aspirin versus LMWH.
- DVT occurred significantly more frequently in the aspirin group compared with the LMWH group (difference 0.80% points; 95% CI, 0.28–1.31)

LIMITATIONS:

- Given the severity of the injury of enrollees in the trial, the investigators allowed eligible patients to receive 2 doses of LMWH before consent could be obtained to enroll in the study.
- Given the multicenter nature of the study and lack of a universal standard, postdischarge duration of thromboprophylaxis varied because of differing hospital protocols.

- Given the open-label design of the trial, there is a chance of surveillance bias for the secondary outcomes.
- The primary outcome was changed after enrollment began before publication and analysis of findings. EBP

Jasbir Kaur, DO
Northeast Georgia Medical Center, Gainesville, GA

The corresponding author is Jasbir Kaur, DO; Jasbir.Kaur@nghs.com.
The author declares no conflicts of interest.

Is high HDL associated with worsening cardiovascular mortality?

Association between High-Density Lipoprotein Cholesterol Levels and Adverse Cardiovascular Outcomes in High-Risk Populations

Liu C, Dhindsa D, Almuwaqqat Z, et al. Association Between High-Density Lipoprotein Cholesterol Levels and Adverse Cardiovascular Outcomes in High-risk Populations. *JAMA Cardiol*. 2022;7(7):672-680. doi:10.1001/jamacardio.2022.0912 DOI 10.1097/EBP.0000000000001961

KEY TAKEAWAY: Both high and low high-density lipoprotein-C (HDL-C) levels are associated with higher mortality risk in individuals with coronary artery disease (CAD).

STUDY DESIGN: Prospective multicenter cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFO: Historically, elevated HDL-C levels are associated with decreased cardiovascular disease (CVD) risk. Newer studies have demonstrated an association between high HDL-C levels with increased cardiac mortality in patients without coronary artery disease (CAD). The authors set out to further investigate the association between HDL-C and CAD.

PATIENTS: Adults with CAD
INTERVENTION: HDL-C levels <40 mg/dL and >60 mg/dL
CONTROL: HDL-C levels 40 to 60 mg/dL
OUTCOME:

Primary outcome: All-cause death
Secondary outcome: Cardiovascular death

METHODS BRIEF DESCRIPTION:

- Investigators analyzed data from the UK Biobank (UKB), which included adults 40 to 72 years old with a history of CAD, and a US-based cohort at Emory (EmCAB) of adults undergoing left heart catheterization for CAD.
- UKB patients had an average age of 62.1 years old, most of whom were men (76.2%) and identified as White (93.8%).
- EmCAB patients had an average age of 63.8 years old, the majority identified as White (73.2%), and over half were current or former smokers.
- HDL-C values and other serum markers were obtained from record review at enrollment.
- Those with an HDL-C level 40 to 60 mg/dL served as the comparator (reference) group.
- The outcomes of all-cause death and cardiovascular death were determined using death registry data (UKB) and telephone interviews, medical records, and public records (EmCAB).

INTERVENTION (# IN THE GROUP)
- UKB: 6,590
- EmCAB: 3,328

COMPARISON (# IN THE GROUP)
- UKB: 7,888
- EmCAB: 2,139

FOLLOW-UP PERIOD:
- UKB: Interquartile range (IQR) 8.0 to 9.7 years
- EmCAB: IQR 4.0 to 10.8 years

RESULTS:
Primary outcome

- In the UKB study, those with HDL-C levels ≤30 mg/dL and >80 mg/dL had a higher risk of all-cause death (adjusted hazard ratio [aHR] 1.3; 95% CI, 1.1 to 1.6 and aHR 2.0; 95% CI, 1.4 to 2.7, respectively) as compared with the reference of 40 to 60 mg/dL.
- In the EmCAB study, those with HDL-C levels ≤30 mg/dL and >80 mg/dL had a higher risk of all-cause death

when compared with groups with HDL-C levels 40 to 60 mg/dL (aHR 1.2; 95% CI, 1.03–1.5 and aHR 1.6; 95% CI, 1.1–2.4, respectively).

Secondary outcomes

- In UKB study, those with HDL-C levels >80 mg/dL had a higher risk of cardiovascular death (aHR 1.7; 95% CI, 1.1–2.7).
- In the EmCAB study, models showed no difference in cardiovascular death at HDL-C levels >80 mg/dL as compared with the reference range.

LIMITATIONS:

- The results were not generalizable to patients without CAD.
- There is potential for misclassification of diagnostic codes.
- Other considerations include incomplete capture of date, relatively homogenous population, and uncertainty as how CAD is defined. EBP

Gagan Malhi, DO
HMH Ocean University Medical Center—Family Medicine, Brick, NJ

The corresponding author is Gagan Malhi, DO; gagan.malhi@hmhn.org.
The author declares no conflicts of interest.

Social determinants of health affecting breast cancer development

Social Determinants of Racial Disparities in Breast Cancer Mortality Among Black and White Women

Babatunde OA, Eberth JM, Felder T, et al. Social Determinants of Racial Disparities in Breast Cancer Mortality Among Black and White Women. *J Racial Ethn Health Disparities.* 2021; 8(1):147-156. doi:10.1007/s40615-020-00766-y DOI 10.1097/EBP.0000000000001931

KEY TAKEAWAY: Unmarried Black women in areas with the lowest socioeconomic status have the highest breast cancer specific mortality risk. Race comparison is not specifically related to development of breast cancer but rather acts as a proxy for systemic racism and social determinants of health.

STUDY DESIGN: Retrospective cohort study.

LEVEL OF EVIDENCE: Level 4, downgraded because of limitation of generalizability and small population size.

BACKGROUND: U.S. national statistics show that Black women have 42% higher breast cancer mortality rates compared with White women. In South Carolina, the disparity is of greater magnitude. This is due in part to social determinants of health including socioeconomic status, health insurance, marital status, county of residence, and enrollment in screening programs.

PATIENTS: Patients with breast cancer.
INTERVENTION: Social determinants of health.
CONTROL: N/A.
OUTCOME: 5-year mortality, 12-year mortality, all-cause survival.

METHODS BRIEF DESCRIPTION:

Data source: South Carolina Central Cancer Registry & Office of Revenue and Fiscal affairs, which maintains administrative medical claims data for private insurance and Medicaid.
Data linkage: Three identifiers including name, DOB, and SSN.
Inclusion/exclusion: Black and White breast cancer cases accounted for 99.28% of all breast cancer incidences and 99.52% of all mortality from breast cancer in the state.
Variables:

- Exposure variable: Race—Black or White.
- Effect modifiers: Age, marital status, county of residence, year of diagnosis, hormone receptor status, enrollment in Best Chance Screening Network, and stage and grade of breast cancer at diagnosis.
- Outcome variable: 5-year mortality, 12-year mortality, all-cause survival.

INTERVENTION (# IN THE GROUP):
2,186 White women;
1,110 Black women.
COMPARISON (# IN THE GROUP): N/A.

FOLLOW-UP PERIOD: 8 years (2002–2010).

RESULTS:

- Risk of mortality was 65% higher in Black women for 12-year breast cancer–specific survival (HR 1.65; 95% CI, 1.38–1.97) and overall survival (HR 1.65; 95% CI, 1.41–1.94) when compared with White women.
- The highest breast cancer specific mortality risk was among Black women who lived in the upstate region (HR 2.96; 95% CI, 1.96–4.45) compared with White women in the Low Country region.
- Unmarried Black women had significantly higher breast cancer mortality risk than married White women (HR 2.31; 95% CI, 1.83–2.91).
- Black women not enrolled in a breast cancer screening program had the greatest risk of mortality as compared to White women who were also not enrolled (HR 1.70; 95% CI, 1.40–2.04).

LIMITATIONS:

- There were no specific criteria for determining the race of the patients in the study.
- This study was limited in cohort diversity and contained low subpopulation counts of Hispanic patients with breast cancer in the data. This limits generalizability of the study because it is more specific to the southeastern U.S. population. EBP

Madison Mitchell, MD
Capital Health Family Medicine Residency Program, Hopewell, NJ

The corresponding author is Madison Mitchell, MD; mmitchell@capitalhealth.org.

The author declares no conflicts of interest.

Is haloperidol alone (rapid tranquilization) an effective and safe treatment for psychosis-induced aggression or agitation?

EVIDENCE-BASED ANSWER

Haloperidol is effective; however, compared with other antipsychotics, it has an increased incidence of extrapyramidal symptoms (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Haloperidol has a longer onset time compared with midazolam and olanzapine (SOR: **B**, RCT).

DOI 10.1097/EBP.0000000000001894

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

A 2017 meta-analysis of 41 randomized controlled trials (RCTs; N=4,933) compared the efficacy and safety of pharmacotherapies including first-generation antipsychotics such as haloperidol, second-generation antipsychotics, and benzodiazepines for the treatment of acute agitation because of psychosis.[1] In these studies, patients were between 18 and 73 years old, 45% male, and, when reported, from mostly inpatient and psychiatric emergency department. Diagnoses included mostly schizophrenia with some bipolar disorder and psychosis not otherwise specified. Researchers excluded patients taking antipsychotics and antidepressants and patients with known alcohol or drug dependency. Medications were given through intramuscular injection or orally. The most common medications included haloperidol (2.5, 5, or 10 mg), olanzapine (2.5, 5, 7.5, or 10 mg), ziprasidone 20 mg, lorazepam 2 mg, and aripiprazole (1, 5, 10, or 15 mg). The primary outcomes included efficacy and safety data on extrapyramidal symptoms (EPS), sedation, and QTc prolongation. Fewer patients were awake in the haloperidol group compared with the placebo group at two hours (2 RCTs, N=220; relative risk [RR] 0.9; 95% CI, 0.8–0.95). Fewer patients in the haloperidol group required repeated rapid tranquilization compared with placebo (4 RCTs, N=660; RR 0.5; 95% CI, 0.4–0.6). Patients treated with haloperidol required fewer injections when compared with aripiprazole (2 RCTs, N=473; RR 0.8; 95% CI, 0.6–0.99) for rapid tranquilization; however, they required more compared with olanzapine at 12 hours (1 RCT, n=60; RR 3.3; 95% CI, 1.7–6.5). A higher risk of EPS was noted with haloperidol compared with placebo (1 RCT, n=180; RR 5.6; 95% CI, 1.4–23), olanzapine (3 RCTs, N=403; RR 8.4; 95% CI, 2.3–31), ziprasidone (2 trials, N=508; RR 19; 95% CI, 7.6–48), and lorazepam (1 RCT, n=60; RR 15; 95% CI, 2–107). Over sedation was reported more in the haloperidol group compared with placebo (2 RCTs, N=313, RR 3.4; 95% CI, 1.4–8). No difference was noted between haloperidol and placebo or olanzapine for QTc interval prolongation.

A 2021 RCT (n=167) compared midazolam, olanzapine, and haloperidol for the management of undifferentiated acute agitation in the emergency department.[2] The study consisted of 167 patients (18–75 years old) with undifferentiated acute agitation requiring parenteral sedation. The study population was 42% to 70% male, with most patients having an underlying mental health disorder. Exclusion criteria included an immediately reversible etiology for agitation, known pregnancy, or acute alcohol withdrawal. Researchers evaluated the time to adequate sedation and the proportion of patients who achieved adequate sedation as primary outcomes. In each treatment arm, patients received an initial 5 mg IM of haloperidol, midazolam, or olanzapine with an additional 5 mg of the same drug, for a maximum dose of 10 mg if needed. Adequate sedation was defined as a score of less than or equal to 2 (mildly aroused, willing to talk reasonably) on a 6-point validated sedation scale (5=highly aroused/violent, 0=asleep). After the initial dose of midazolam, olanzapine, or haloperidol, 52%, 34%, and 21% of patients were adequately sedated at 10 min and 98%, 87%, and 97% at 60 minutes, respectively (*P* values not reported). When comparing median time to sedation, midazolam resulted in faster sedation than olanzapine (8.5 vs 12 minutes; *P*=.03) and haloperidol (8.5 vs 23 minutes; *P*=.002), but no difference was noted between haloperidol and olanzapine. No differences were noted in adverse events (oxygen desaturation, QTc prolongation, or dystonia) between the three treatment groups. EBP

Amanda Jamal, MD
Kimberly Lee Kin, DO
Harjot Hayer, MD
Valley Family Medicine Residency, Modesto, CA

The corresponding author is Amanda Jamal, MD, ajamal@schsa.org
The authors declare no conflicts of interest.

References

1. Ostinelli EG, Brooke-Powney MJ, Li X, Adams CE. Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation). *Cochrane Database Syst Rev*. 2017; 7(7): CD009377. [STEP 1]
2. Chan EW, Lao KSJ, Lam L, et al. Intramuscular midazolam, olanzapine, or haloperidol for the management of acute agitation: a multi-centre, double-blind, randomised clinical trial. *E Clin Med*. 2021; 32:100751. [STEP 2]

Is CBT an effective intervention for weight loss?

EVIDENCE-BASED ANSWER

Cognitive behavioral therapy (CBT) alone, and as an adjunct to diet and exercise, leads to modest weight loss in overweight and obese adult patients. CBT for weight loss also modestly improves cognitive restraint and disordered eating behaviors (SOR: A, meta-analysis of randomized controlled trials).

DOI 10.1097/EBP.0000000000001898

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

A 2018 meta-analysis of 12 randomized controlled trials (RCTs; N=6,805) evaluated the effect of cognitive behavioral therapy (CBT) on weight loss and psychological outcomes.[1] The trials included nonmilitary overweight or obese adults (predominantly female, mean age, 45 years old). Researchers excluded patients with comorbid diseases that conferred greater illness morbidity than obesity, such as cardiovascular disease, chronic obstructive pulmonary disease, cancer, or severe mental disorders. Patients received CBT or nutrition, physical activity, usual care, or a behavior change technique over four to 48 weeks. Most studies conducted CBT sessions weekly (10 of 12 trials), whereas two studies had biweekly sessions and monthly sessions respectively (mean 27 CBT sessions). The primary outcome was weight loss, and the secondary outcomes were psychological results such as emotional eating, cognitive restraint, binge eating, depressive symptoms, and anxiety. Researchers evaluated emotional eating using the Dutch Eating Behavior Questionnaire (DEBQ), a self-reported 33-item questionnaire assessing the three distinct behavior domains of emotional eating, external eating, and dietary restraint. Researchers measured cognitive restraint by the Three Factor Eating Questionnaire, a self-reported 51-item questionnaire assessing three dimensions of eating behavior (cognitive restraint, disinhibition, and hunger). Researchers measured binge eating by the number of binges in 28 days. Finally, they measured depressive and anxiety symptoms by eight different validated questionnaires. The patients receiving CBT experienced an average weight loss of –1.7 kg (12 trials, N=6,805; 95% CI, –2.5 to –0.86 kg, I^2=86%) more than the other interventions. The CBT group also improved cognitive restraint (6 trials, N=666; standard mean difference [SMD] 0.72; 95% CI, 0.33–1.1) and decreased emotional eating (6 trials, n=371; SMD –0.32; 95% CI, –0.49 to –0.16). Change in depressive symptoms did not differ between the groups, and the differences in anxiety and binge eating could not be calculated. Limitations included survey heterogeneity, the use of moderation analyses, half of the studies lacking an intention-to-treat analysis, potential overlap between CBT groups and behavioral interventions, lack of follow up analyses, and publication bias.

A 2021 low-quality RCT (n=43) evaluated the effect of interdisciplinary therapy plus CBT (IT+CBT) on anthropometric profiles, eating behaviors, anxiety, depression, and quality of life for obese patients.[2] Patients were predominantly female, 30 to 50 years old, with a BMI of 30 to 40 kg/m^2. Researchers excluded patients with unstable medical conditions, pregnancy, current recreational drug use, pharmacotherapy for obesity, or previous bariatric surgery. Patients were divided into three groups: IT+CBT, education and health (EH), or physical exercise (PE). The EH group received monthly education and health lectures, whereas the PE group received 60-minute workout sessions three times per week. The IT+CBT group received monthly education and health lectures and 60-minute workout sessions three times per week in addition to a total of 28 one-hour

CBT sessions over 30 weeks. The outcomes were anthropometric measures, eating behaviors, anxiety, depression, and quality of life measurements. Researchers measured eating behaviors with the DEBQ. They quantified anxiety and depression using the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI), respectively, which are 21-item self-reported measures scored on a scale of zero to 63, with higher scores indicating worse anxiety or depression. Researchers measured quality of life by the World Health Organization Quality of Life Brief assessment, a 26-item self-administered questionnaire, scaled on a score of zero to 100, with higher scores indicating better quality of life. Researchers analyzed pre- and postintervention data using the Wilcoxon test for paired samples and compared results between the groups using the Kruskal–Wallis test. The average weight loss in the IT+CBT group was 3.1 kg (95% CI, –3.9 to –2.2) and 1.4 kg in the PE group (95% CI, –2.1 to –0.81). Although both the IT+CBT group and PE group had significant weight loss, there was no difference in weight loss between the two groups. The EH group did not have a significant weight reduction. IT+CBT also improved eating behaviors (total change on DEBQ= –8.4; 95% CI, –8.5 to –8.3) and depressive symptoms (total change on BDI= –10; 95% CI, –13 to –7) but not quality of life and anxiety symptoms. Limitations included small sample size, a 56% participant dropout rate without an intention-to-treat analysis, reporting bias, bundling CBT with all other interventions, and the lack of any identifiable clinical impacts of improvements in weight, eating behaviors, and depressive symptoms. EBP

Catherine LaRowe, DO
Matthew Hess, DO
Nellis Air Force Base, Nellis AFB, NV

Corresponding author: Catherine LaRowe, DO; catherine.e.larowe.mil@health.mil

The authors declare no conflicts of interest.

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

References

1. Jacob A, Moullec G, Lavoie KL, et al. Impact of cognitive-behavioral interventions on weight loss and psychological outcomes: a meta-analysis. *Health Psychol*. 2018; 37(5): 417–432. [STEP 1]
2. Moraes ADS, Padovani RDC, La Scala Teixeira CV, et al. Cognitive behavioral approach to treat obesity: a randomized clinical trial. *Front Nutr.* 2021; 8:611217. [STEP 2]

In men with prostate cancer, is androgen deprivation therapy associated with increased cardiovascular risk?

EVIDENCE-BASED ANSWER

Androgen deprivation therapy (ADT) in men with prostate cancer is not associated with an increased risk of cardiovascular mortality, but there may be a correlation with nonfatal cardiovascular disease and events (SOR: **B**, systematic reviews with meta-analyses of cohort studies and randomized controlled trials [RCTs]). All-cause mortality is improved in prostate cancer patients treated with ADT and therefore should be considered in shared decision making (SOR: **A**, systematic review with meta-analysis of RCTs).

DOI 10.1097/EBP.0000000000001919

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

A 2019 systemic review and meta-analysis of 15 cohort studies (N=611,397) and four randomized controlled trials (RCTs; N=9,824) examined the incidence of acute myocardial infarction (AMI), cardiovascular disease (CVD), and sudden cardiac death (SCD) associated with androgen deprivation therapy (ADT) in adult males treated for prostate cancer versus nonusers of ADT.[1] Multiple inclusion criteria were used, although the primary ones were that studies had to prespecify outcomes of SCD, CVD, and AMI, baseline cardiac comorbidities needed to be reported, and sufficient data had to be present to calculate 95% CIs. ADT included peripheral antiandrogens, gonadotropin-releasing hormone (GnRH) agonists, and orchiectomy. CVD was defined as the onset of any adverse cardiac event, signs, or symptoms. Patients were followed for 1 to 22 years. ADT was associated with an increased risk of AMI and CVD (**TABLE 1**).

TABLE. Cardiovascular risk of androgen deprivation therapy (vs no ADT) in patients treated for prostate cancer

Outcome	No. of Studies	No. of patients (n)	RR or OR (95% CI)	I^2	Interpretation
AMI[1]	8	157,784	**RR 1.19 (1.02–1.39)**	95%	Favors *no* ADT
AMI[3]	4	122,969	**OR 2.01 (1.90–2.13)**	100%	Favors *no* ADT
AMI (*just RCTs*)[3]	2	8,211	OR 1.23 (0.92–1.64)	0%	No difference
CVD[1]	13	542,220	**RR 1.25 (1.11–1.40)**	99%	Favors *no* ADT
SCD[1]	8	186,399	RR 1.13 (0.92–1.38)	79%	No difference
Non-fatal CV events[3]	5	116,074	OR 1.24 (0.89–1.72)	98%	No difference
Non-fatal CV events (*just RCTs*)[3]	3	1,316	**OR 1.55 (1.09–2.20)**	0%	Favors *no* ADT
CV mortality[2]	8	4,141	RR 0.93 (0.79–1.10)	0%	No difference
CV mortality[3]	6	56,550	OR 1.33 (0.89–1.98	90%	No difference
All-cause mortality[2]	11	4,805	**RR 0.86 (0.80–0.93)**	41%	Favors ADT

The bolded values identify outcomes that are statistically significant. ADT=androgen deprivation therapy; AMI=acute myocardial infarction; CV=cardiovascular; CVD=cardiovascular disease; I^2=assessment of heterogeneity (lower % equals less heterogeneity); OR=Odds Ratio; RCT=randomized controlled trial; RR=Risk Ratio; SCD=sudden cardiac death.

Sudden cardiac death was not increased in the patients receiving ADT. Some key limitations of this meta-analysis included the fact that studies where CVD was not explicitly defined were included, the lack of an assessment for preexisting cardiac disease did not occur in most studies, many studies' data were not included completely leading to review authors to extract data manually, and heterogeneity (as calculated by I^2) was considerable.

A 2011 meta-analysis of 11 RCTs (N=4,085) specifically examined cardiovascular and all-cause mortality associated with ADT treatment in patients (median ages 64–73) diagnosed with nonmetastatic and non–hormone-refractory prostate cancer compared with patients not treated with ADT.[2] Only RCTs that predominantly used GnRH agonists and included adequate information on cardiovascular death were included. Three RCTs included in this meta-analysis were also included in the first reference (above). Median follow-up periods ranged from 7.6 to 13 years. No difference in cardiovascular mortality between patients on ADT and the control group were noted (**TABLE**). As opposed to the previous reference (above), no significant heterogeneity was noted. When all-cause mortality was assessed, those on ADT faired significantly better. Limitations included lack of stratification of preexisting cardiovascular comorbidity and the inability to exclude the possibility that cardiovascular deaths could have occurred earlier in men treated with ADT.

A 2015 systematic review and meta-analysis of four cohort studies (N=126,898) and nine RCTs (N=16,799) evaluated the risk of cardiovascular morbidity and mortality in patients diagnosed with prostate cancer and treated with ADT (or not) for at least six months.[3] This study had four RCTs and two cohort studies that overlapped with the previous two meta-analyses. Patients had a median follow-up of 3.8 to 10 years. Patients in the treatment group received luteinizing hormone–releasing hormone analogs, peripheral antiandrogens, or orchiectomy and were followed for at least six months. Although the overall risk of AMI was significantly increased in the ADT group, no difference was noted in cardiovascular mortality or nonfatal cardiovascular events (defined as arrhythmias, angina pectoris, nonfatal stroke, nonfatal AMI, and heart failure) between the ADT group and the control group (**TABLE**). When subgroup analysis including only the RCTs was performed, no difference in AMI or stroke was noted between groups. EBP

Jenna Pfleeger, MD
Ehab Molokhia, MD, MPH
Jordan Harrison, DO
Hannah Marshall, DO
Deep Patel, MD
University of South Alabama Family Medicine Residency Program, Mobile, AL

The corresponding author is Jenna Pfleeger; jpfleeger@health.southalabama.edu
The authors declare no conflicts of interest.

References

1. Liang Z, Zhu J, Chen L, et al. Is androgen deprivation therapy for prostate cancer associated with cardiovascular disease? A meta-analysis and systematic review. *Andrology*. 2020; 8(3):559–574. [STEP 1]
2. Nguyen PL, Je Y, Schutz FAB, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. *JAMA*. 2011; 306(21):2359–2366. [STEP 1]
3. Carneiro A, Sasse AD, Wagner AA, et al. Cardiovascular events associated with androgen deprivation therapy in patients with prostate cancer: a systematic review and meta-analysis. *World J Urol.* 2015; 33(9):1281–1289. [STEP 3]

Do orthostatic vital signs have utility in the evaluation of syncope?

EVIDENCE-BASED ANSWER

Yes, in certain scenarios. Positive orthostatic vital signs (OVS) in the setting of certain risk factors, such as age >75 years old, Parkinson's disease, or use of antihypertensive medications, diuretics, nitrates, or digoxin, favors orthostatic hypotension (OH) as the source of syncope (SOR: **A**, based on consistent findings from 2 good-quality diagnostic cohort studies). In patients experiencing syncope, if OH is determined to be the cause, survival is improved compared with those with a cardiac cause of their syncope (SOR: **B**, based on 1 good-quality diagnostic cohort study).

DOI 10.1097/EBP.0000000000001748

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

A 2009 prospective cohort study of patients >65 years old (n=259, 57% female, mean age 79 years old) who were admitted to one of 11 Italian Emergency Departments (EDs) because of transient loss of consciousness evaluated the prevalence of syncope resulting from orthostatic hypotension (OH).[1] Blood pressure measurements were taken after five minutes of lying supine and after one and three minutes of standing. A decrease in systolic blood pressure (SBP) of 20 mmHg or more, or SBP of <90 mmHg was considered to be OH. Syncope resulting from OH was defined as OH with syncope or presyncope. The study found that performing orthostatic vital signs (OVS) in the initial evaluation diagnosed OH as the cause of syncope in 22 patients (8.5%). Syncope resulting from OH was ultimately diagnosed in 10 more patients (32 total, or 12%) after additional testing with a tilt table (diagnosed if a fall in SBP was noted within 3 minutes of a 60-degree tilt in association with presyncope or syncope; n=8), 24-hour ambulatory blood pressure monitoring (n=1), and ongoing positional vital signs testing (n=1). Of note, a multivariate analysis found that Parkinson's disease and use of nitrates or diuretics were additional independent clinical risk factors associated with syncope resulting from OH (see **TABLE 1**).

TABLE 1. Select clinical characteristics of patients >65 years old presenting to an Emergency Department experiencing syncope with or without orthostatic hypotension[1]

Clinical characteristic	Syncope *with* orthostatic hypotension, n (%) 32 total patients	Syncope *without* orthostatic hypotension, n (%) 227 total patients	*P*
Parkinson's disease[1]	4 **(12%)**	5 **(2.2%)**	**.003**
Use of diuretics	12 **(38%)**	56 **(25%)**	**.049**
Use of nitrates	10 **(31%)**	17 **(7.5%)**	**<.001**
Use of digoxin	6 **(19%)**	15 **(6.6%)**	**.018**
Coronary artery disease	10 (31%)	51 (23%)	ns
Hypertension	20 (63%)	126 (56%)	ns
Hypertension with LVH	6 (19%)	47 (21%)	ns
Valvular heart disease	1 (3.1%)	15 (6.6%)	ns
Ischemic cerebral disease	7 (22%)	31 (14%)	ns
Diabetes	3 (9%)	22 (10%)	ns

Bold indicates significant difference. LVH=left ventricular hypertrophy; n=number of study participants; ns=not significant.

A 2019 secondary analysis of a multicenter prospective cohort study of patients 60 years old or older (n=1,974, 49% female, mean age 72 years old) who presented to one of 11 U.S. academic EDs with syncope or near-syncope evaluated whether OVSs were predictive of composite 30-day outcome for 22 serious adverse events (eg, myocardial infarction, stroke, cardiac dysrhythmias)[2]. Positive OVSs were defined as an SBP drop of ≥20 mmHg after two minutes of standing, a drop of 10 mmHg immediately upon standing, or presyncope immediately upon standing. Two hundred ninety-five study subjects (15%) experienced one of the serious adverse event composite outcomes. No difference was noted in the composite for adverse outcomes at 30 days between those with positive OVS compared with those with negative OVS (15% each; unadjusted odds ratio 1.05; 95% CI, 0.81–1.4).

A 2002 prospective cohort study of patients 18 years old or older who presented with syncope (n=650) to an ED in Switzerland evaluated the prevalence of syncope resulting from OH and the clinical characteristics of patients diagnosed with OH.[3] Blood pressure measurements were taken after five minutes of lying supine; immediately upon standing; and after 1, 2, 3, 5, and 10 minutes of standing. Syncope was considered to be resulting from OH when SBP dropped by 20 mmHg or more, and syncope or presyncope occurred if SBP dropped below 90 mmHg with or without symptoms, or if a prehospital SBP of 80 mmHg or less was documented and intravenous fluid resuscitation had been given before arrival. Eleven percent (n=71) of patients could not be evaluated because of inability to stand up (eg, hip fracture) or because of other contraindications (eg, dysrhythmia or acute myocardial infarction). Six-month interval follow-up occurred for 18 months total, with 6% of patients lost to follow-up. OH was the cause of syncope in 24% of patients (n=156) presenting to the ED. At the follow-up period of 18 months, patients diagnosed with OH demonstrated an overall mortality rate of 9% (95% CI, 5%–13%), which was significantly lower than that of patients identified as having a cardiac cause of syncope (26%; 95% CI, 16%–36%; *P*=.001). Patients with vasovagal syncope or OH were the two largest categories of syncope in this study, representing 398 of 650 patients (61%). When compared directly with patients diagnosed with vasovagal syncope, those with OH had notable correlations with certain comorbid diagnoses, more hypotensive medication use, and abnormal ECGs (see **TABLE 2**).

TABLE 2. Select clinical characteristics of adult patients presenting to an Emergency Department experiencing syncope attributed to orthostatic hypotension or vasovagal syncope[2]

Clinical characteristic	Syncope resulting from orthostatic hypotension, n (%) 156 total patients	Vasovagal syncope, n (%) 242 total patients	*P*
Age ≥75 years old	**55 (35%)**	**49 (20%)**	**<.01**
Male gender	73 (47%)	111 (46%)	ns
Diabetes mellitus	**17 (11%)**	**15 (6%)**	**.01**
Coronary artery disease	**25 (16%)**	**20 (8%)**	**.05**
Organic heart disease	**42 (27%)**	**31 (13%)**	**.01**
Congestive heart failure	**14 (9%)**	**10 (4%)**	**.05**
Hypertension	**66 (42%)**	**58 (24%)**	**<.01**
Taking one or more antihypertensive medications	**122 (78%)**	**68 (28%)**	**<.01**
One hypotensive medication	**80 (51%)**	**45 (19%)**	**<.01**
≥2 hypotensive medications	**42 (27%)**	**23 (10%)**	**<.01**
Abnormal ECG[a]	**25 (16%)**	**15 (6%)**	**<.01**
Hospitalization	**53 (34%)**	**19 (8%)**	**<.01**

Bold indicates significant difference. [a] Abnormal ECG=note, exact definition too extensive to contain in this text. ECG=electrocardiogram; n=number of study participants; ns=not significant.

A 2017 evidence-based guideline from the American College of Cardiology and the American Heart Association recommended that OVS be measured in all patients who present with syncope (Class of Recommendation I, Level of Evidence B).[4] They define OH as a drop in SBP of ≥20 mmHg or DBP ≥10 mmHg upon assuming an upright posture. The authors noted that developing any risk-stratification schemes regarding outcomes in those with syncope is difficult, given the inclusion of patients with both benign and life-threatening causes of syncope in prospective studies. EBP

Eric Lemister, DO
Kayla Watson, MD
Stephanie Fulleborn, MD
Eglin Air Force Base Family Medicine Residency Program, Eglin AFB, FL

The corresponding author is Stephanie Fulleborn; stephanie.t.fulleborn.mil@mail.mil or stfulleborn@gmail.com
The authors declare no conflict of interest.
The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the U.S. Air Force Medical Service, the Air Force at large, the Defense Health Agency, or the Department of Defense.

References

1. Mussi C, Ungar A, Salvioli G, et al. Orthostatic hypotension as cause of syncope in patients older than 65 years admitted to emergency departments for transient loss of consciousness. *J Gerontol A Biol Sci Med Sci*. 2009;64A:801-806. [STEP 2]
2. White JL, Hollander JE, Chang AM, et al. Orthostatic vital signs do not predict 30 day serious outcomes in older emergency department patients with syncope: a multicenter observational study. *Am J Emerg Med.* 2019;37:2215-2223. [STEP 2]
3. Sarasin FP, Louis-Simonet M, Carballo D, et al. Prevalence of orthostatic hypotension among patients presenting with syncope in the ED. *Am J Emerg Med.* 2002;20:497-501. [STEP 2]
4. Shen W-K, Sheldon RS, Benditt DG, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2017;70:e39–110. [STEP 5]

Does vitamin B2 help with reducing migraine frequency and severity?

EVIDENCE-BASED ANSWER

Vitamin B2 supplementation reduced frequency and severity of migraines when compared with placebo (SOR: **A**, meta-analysis). Vitamin B2 (100 mg daily) is noninferior to propranolol and causes fewer side effects (SOR: **B**, randomized controlled trial [RCT]). Vitamin B2 (400 mg/d) is also noninferior to sodium valproate and again causes fewer side effects (SOR: **B**, RCT).

DOI 10.1097/EBP.0000000000001742

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

A 2021 systematic review and meta-analyses of eight randomized controlled trials (RCTs) and one clinical controlled trial (N=673) evaluated vitamin B2 for migraine prophylaxis.[1] Studies were conducted in Germany, India, America, Iran, and Belgium. Inclusion criteria included adult patients with migraine, with or without aura, using vitamin B2 alone or vitamin complex (containing vitamin B2) as the intervention. Outcomes included the number of migraine days, duration, frequency, and pain scores. Vitamin B2 doses ranged from 100 to 400 mg orally once a day for three months. Follow-up ranged from 1 to 6 months. Meta-analysis performed on four RCTs found vitamin B2 reduced migraine frequency by about two attacks per month compared with placebo (standard mean difference [SMD, given graphically] about −0.4; 95% CI, −0.59 to −0.28). Meta-analysis on four RCTs found vitamin B2 reduced migraine duration by 0.4 to 10 h compared with placebo (SMD about −0.25; 95% CI, −0.400 to −0.085). Meta-analysis on five RCTs found no reduction in headache pain score compared with placebo at month 1, 2, 4, or 6, although reduction was observed in pain score month 3. A limitation of the meta-analysis was variation between compared studies leading to high levels of heterogeneity for each outcome.

An open-label RCT in 2011 (n=100) compared propranolol with vitamin B2 for reducing migraine

frequency and severity.[2] Patients between ages 18 and 65 years and sex-matched, with a history of migraine with or without aura, were recruited from two outpatient neurology clinics and randomly assigned to two groups, receiving either propranolol 80 mg daily (standard prophylaxis) or vitamin B2 100 mg daily. Frequency and severity of attacks, as well as duration, disability, and side effects, were measured at 1, 3, and 6 months using a migraine diary, visual analog scale (VAS, range 0–10), and the migraine disability assessment test (range 0–90). B2 and propranolol both decreased migraine frequency at 3 and 6 months with no difference between them (4.0 episodes/mo to 2.3 with propranolol treatment and 4.0 to 2.3 episodes/mo with vitamin B2, $P=.355$). However, propranolol treatment was associated with a decrease in frequency by one month (3.3 episodes/mo with propranolol vs 3.9 episodes/mo with vitamin B2, $P<.001$). Severity was decreased similarly in both groups (change in VAS score at 3 months was 5.3–4.0 with propranolol and 4.9–3.6 with vitamin B2). Duration and disability scores were also equivalently decreased in both groups at three months. B2 had fewer side effects compared with the propranolol group (22% vs 44%, $P=.035$). The primary limitation of this study was its open label format.

A single-blind (physicians were unblinded, while analysis was performed blinded) RCT (n=90) in 2015 compared vitamin B2 with sodium valproate for migraine prophylaxis.[3] Patients between 15 and 55 years old, with a history of migraine with or without aura, were recruited for the study. Patients were randomized to receive vitamin B2 400 mg/d or sodium valproate 500 mg/d for 12 weeks. Patients were reevaluated at 4, 8, and 12 weeks with assessment of headache frequency, severity, duration, and nausea/vomiting as well as medication side effects. Patients self-recorded headache days for each month and used a 0 to 10-point VAS for pain. Frequency and severity of migraines decreased with both treatments, but no difference was observed between the two groups. Frequency decreased from 9.2 episodes/mo to 2.4 with vitamin B2 and 6.5 episodes/mo to 2.1 with valproate. The severity decreased by 71.2% with vitamin B2 and 76.2% with valproate. The duration of headaches and nausea/vomiting symptoms also decreased but without much variation between the two groups. However, vitamin B2 caused fewer side effects than valproate (2.3% vs 17.7%, $P=.005$). The single-blind design and a wide baseline difference in headache frequency limited the strength of this study. EBP

Alexander Phan, DO
Jana Mooster, MD, PhD
Dale Morris, MD, MPH
Valley Family Medicine Residency, Modesto, CA

The corresponding author is Alexander Phan, DO; aphan@schsa.org.
The authors declare no conflict of interest.

References

1. Chen YS, Lee HF, Tsai CH, et al. Effect of vitamin B2 supplementation on migraine prophylaxis: a systematic review and meta-analysis. *Nutr Neurosci.* 2021:1–12. [STEP 1]
2. Nambiar NJ, Aiyappa C, Srinivasa R. Oral riboflavin versus oral propranolol in migraine prophylaxis: an open label randomized controlled trial. *Neurol Asia*. 2011;16(3):223–229. [STEP 2]
3. Rahimdel A, Zeinali A, Yazdian-Anari P, Hajizadeh R, Arefnia E. Effectiveness of vitamin B2 versus sodium valproate in migraine prophylaxis: a randomized clinical trial. *Electron Physician*. 2015;7(6):1344–1348. [STEP 2]

Does income inequality affect pregnancy-related mortality more in Black women?

EVIDENCE-BASED ANSWER

It is unclear. In more deprived U.S. counties, Black women have a 70% higher maternal mortality risk and White women a 104% higher maternal mortality risk compared with women in more affluent counties (SOR: **B**, ecological study). However, another analysis demonstrated a higher maternal mortality among Black women compared with White women with increasing statewide measures of inequality (SOR: **B**, cross-sectional study).

DOI 10.1097/EBP.0000000000001941

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

A 2021 statistical analysis of long-term trends from the National Vital Statistics System data assessed the relationship between maternal mortality rates and sociodemographic factors for women in the United States.[1] Data were collected from national birth and death registries, but the total number of patients was not reported. Maternal deaths in this study were defined as "those related to or aggravated by pregnancy or pregnancy management, and which occur during or within 42 days after the end of pregnancy." Maternal deaths and rates for racial groups and ethnic subgroups, maternal education, marital status, nativity/immigrant status, and maternal age were computed. More details regarding inclusion and exclusion criteria were not found. U.S. counties were divided into groups based on depravation level. Rate of change in maternal mortality according to deprivation level was calculated and analyzed. Women in the most deprived areas had 120% higher maternal mortality risk compared with women in the most affluent areas from 2014 to 2018 (relative risk [RR] 2.2; 95% CI, 2.0–2.4). Black women in the most deprived counties had a 70% higher maternal mortality risk (RR 1.70; 95% CI, 1.36–2.04), and White women had a 104% higher maternal mortality (RR 2.04; 95% CI, 1.8–2.3) compared with more affluent areas from 2014 to 2018. Maternal mortality rates were reported but not statistically analyzed in the study for American Indian women (20 vs 55 per 100,000), Asian and Pacific Islander women (11 vs 28 per 100,000), and Hispanic women (11 vs 13 per 100,000). The overall maternal mortality rate was higher for Black women compared with White women from 2013 to 2017 (48.2 per 100,000 live births vs 21.6 per 100,000). This study was limited by suspected underreporting of maternal mortality on the death certificates of underrepresented minorities.

A 2019 retrospective review examined the association between income inequality and pregnancy-related mortality among all Black and White women across the United States from 2011 to 2015.[2] Data were collected from the National Vital Statistics System, but the total number of patients was not reported. Pregnancy-related mortality was defined as death while pregnant or within a year after the end of pregnancy from any cause related to or aggravated by the pregnancy or its management. Total population and race-specific pregnancy-related mortality were both calculated in states with at least five deaths within the five-year period. As a result, Alaska, Delaware, and DC were excluded from the analysis of the White population, and 20 states were excluded from the analysis of the Black population. Analyses for the total, White, and Black populations were performed with the samples of 51, 48, and 31 states, respectively. Income inequality was defined as the degree of unequal distribution of income within a population. The Gini coefficient was used as an indicator of income inequality, ranging from 0 to 1 with lower values representing more equitable distribution of income. Black women had a 5.3 higher absolute (95% CI, 1.8–8.9) and 0.14 higher relative (95% CI, 0.00–0.28) risk per 100,000 in pregnancy-related mortality compared with White women with increased current income inequality. There was no difference between Black and White women when comparing state median income, college graduates, or unemployment. EBP

Anne Nash, MD
Alleen Richards, MD
SLU Southwest Illinois Family Medicine Residency Program, O'Fallon, IL

The corresponding author is Anne Nash, MD; anash@sihf.org.
The authors declare no conflicts of interest.

References

1. Singh GK. Trends and social inequalities in maternal mortality in the United States, 1969-2018. *Int J MCH AIDS*. 2021; 10(1):29–42. [STEP 3]
2. Vilda D, Wallace M, Dyer L, Harville E, Theall K. Income inequality and racial disparities in pregnancy-related mortality in the US. *SSM Popul Health*. 2019; 9:100477 [published correction appears in SSM Popul Health. 2020; 12:100714. [STEP 3]

Does the 52-mg levonorgestrel intrauterine device have the same efficacy as the copper intrauterine device when used for postcoital ("emergency") contraception?

EVIDENCE-BASED ANSWER

Yes. The 52-mg levonorgestrel intrauterine device (IUD) and copper IUD are equally effective for emergency contraception (SOR: **B**, single randomized controlled trial [RCT]). Both IUDs prevent pregnancy without the use of backup contraception in patients who have sexual intercourse within the first week of placement (SOR: **C**, secondary analysis of the same RCT as above).

DOI 10.1097/EBP.0000000000001750

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

A multicenter, randomized, noninferiority single-blinded trial (n=711) compared the levonorgestrel 52-mg intrauterine device (IUD) with a 380-mm^2 copper IUD on the effectiveness of each as emergency contraception[1]. Patients had a mean age of 24 years old, were mostly White or Hispanic from the U.S., with a body mass index of less than 25 kg/m^2, and were requesting emergency contraception after unprotected sexual intercourse up to five days before intake. Individuals who were breastfeeding, had vaginal bleeding, were currently using contraception, or had untreated sexually transmitted infections were excluded. The primary outcome was a positive urine pregnancy test one month after insertion. Pregnancy rates were 1 in 317 in the levonorgestrel group and zero in 321 in the copper IUD group. No significant difference in rates was noted between the levonorgestrel IUD and the copper IUD groups (absolute difference 0.3%; 95% CI, –0.9% to 1.8%). Side effects were minimal, included mostly bleeding, cramping, and pain and did not differ between groups. Limitations included a low number of diverse patients represented and lack of provider blinding.

A secondary analysis (n=286) of the above described randomized controlled trial compared 52-mg levonorgestrel IUD with 380-mm^2 copper IUD on effectiveness of emergency contraception.[2] This study is summarized separately because this secondary analysis examined patients who had the IUD placed greater than seven days from their last menstrual period and who reported having unprotected intercourse within seven days of placement. After one month, a urine pregnancy test was performed. Inclusion and exclusion criteria were similar to the original study and are summarized above. After one month, no difference was noted in pregnancy rates between the levonorgestrel IUD group (0%; 95% CI, 0.0%–2.6%) and the copper IUD group (0%; 95% CI, 0.0%–2.5%). No harms of intervention were reported. Major limitations included the study being underpowered and inconsistent urine testing timing. EBP

Deja Finley, PharmD
Nazanin Kheirkhahan, MD
Andrea Richards, MD
Tyler Wright, MD
Southern Illinois University School of Medicine Family Medicine Residency Program, Alton, IL

The corresponding author is Deja Finley; definle@siue.edu.
The authors declare no conflict of interest.

References

1. Turok DK, Gero A, Simmons RG, et al. Levonorgestrel vs. copper intrauterine devices for emergency contraception. *N Engl J Med*. 2021;384(4):335-344. [STEP 2]
2. Fay KE, Clement AC, Gero A, et al. Rates of pregnancy among levonorgestrel and copper intrauterine emergency contraception initiators: implications for backup contraception recommendations. *Contraception*. 2021;104:561-566. [STEP 4]

Does the use of curcumin increase the likelihood of remission in patients with inflammatory bowel disease?

EVIDENCE-BASED ANSWER

Adding curcumin to mesalamine for ulcerative colitis increases the likelihood of clinical remission by approximately three-fold and endoscopic remission by approximately two-fold (SOR: **B**, meta-analysis of small, heterogeneous randomized controlled trials [RCTs]). Theracurmin, a curcumin derivative, may improve clinical but not endoscopic remission rates in patients with Crohn disease (SOR: **C**, underpowered RCT). Experts have not recommended curcumin for treating ulcerative colitis sighting a lack of evidence (SOR: **C**, clinical guidelines).

DOI 10.1097/EBP.0000000000001777

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

A 2020 systematic review and meta-analysis analyzed seven placebo-controlled randomized controlled trials (RCTs; N=380) assessing curcumin as an adjunctive therapy in patients with ulcerative colitis (UC).[1] Trials were from India (4 RCTs, N=185), Iran (1 RCT, n=56), Israel (1 RCT, n=50), and Japan (1 RCT, n=89). Patients were predominantly male (58%; 2 studies omitted patients' sex) with mean ages ranging from 33 to 45 years old. Four studies detailed the extension of colonic disease as proctitis (n=48), left-sided colitis (n=118), and pancolitis (n=41). Trials used oral (6 RCTs, N=335) or rectal (1 RCT, n=45) curcumin dosed between 100 and 10,000 mg/d. Both intervention and control groups also received mesalamine, and follow-up ranged from 4 to 24 weeks. Outcomes included clinical and endoscopic remission, measured using standardized scoring systems with established thresholds to determine remission. When used as adjective therapy with mesalamine, curcumin use was significantly associated with clinical (5 trials, N=282; odds ratio [OR] 2.9; 95% CI, 1.5–5.5) and endoscopic (5 trials, N=235; OR 2.3; 95% CI, 1.2–4.6) remission. Curcumin dosage did not have a significant predictive effect on outcomes. Limitations included the inability to analyze results based on comorbidities and moderately high heterogeneity attributed to differences in disease severity indices, dosages of curcumin, and route of curcumin administration. However, the meta-analysis found all studies to be of high quality.

A 2020 multicenter double-blind RCT from Japan examined the effectiveness of Theracurmin, a highly bioavailable curcumin derivative, in 30 patients with active mild-to-moderate Crohn disease.[2] The patients were on average 35 years old who had Crohn disease for eight years; 70% were male, 60% had perianal disease, 90% were concurrently taking a 5-aminosalicylate drug, and 33% were on an immunomodulator. Patients were randomly assigned to take 180 mg BID of Theracurmin (n=20) or placebo (n=10) for 12 weeks. Secondary outcomes included clinical and endoscopic remission, measured using standardized scoring systems with recognized definitions of remission. Clinical remission rates for patients taking Theracurmin compared with placebo were 35% and 0%, respectively, at four weeks (P=.03), and 40% and 0%, respectively, both at 8 (P=.02) and 12 (P=.02) weeks. However, endoscopic remission rates at 12 weeks were not significantly different for patients taking Theracurmin compared with placebo (15% vs 0%, P=.22). The researchers reported no serious adverse events. Limitations included an inability to perform a power analysis because of lack of previous data on the expected effect of Theracurmin.

A 2019 evidence- and consensus-based guideline from the American Gastroenterological Association was unable to recommend using curcumin for the management of mild-to-moderate UC because of very low-quality evidence concerning its ability to maintain disease remission (no recommendation based on knowledge gap).[3] The guideline authors expressed concern that although less-conventional therapies such as curcumin, probiotics, and fecal microbiota transplantation seem to be safe, their use may risk delaying treatment with other agents proven to be effective.

Similarly, a 2019 evidence- and consensus-based guideline developed by the American College of Gastroenterology was unable to recommend complementary therapies such as curcumin and probiotics for treating UC in adults, noting that these agents required further study with adequate power and clarification of endpoints (no recommendation or evidence quality provided).[4] EBP

Paula Trepman, MD, MPH
Christine Luu, MD
Iman Majd, MD, MS, EAMP, LAc
University of Washington, Seattle, WA

The corresponding author is Iman Majd, MD, MS, EAMP, LAc; imanmajd@uw.edu.
The authors declare no conflicts of interest.

References

1. Chandan S, Mohan B, Chandan O, et al. Curcumin use in ulcerative colitis: is it ready for prime time? A systematic review and meta-analysis of clinical trials. *Ann Gastroenterol.* 2020; 33(1):53-58. [STEP 1]
2. Sugimoto K, Ikeya K, Bamba S, et al. Highly bioavailable curcumin derivative ameliorates Crohn's disease symptoms: a randomized, double-blind, multicenter study. *J Crohns Colitis*. 2020;14(12):1693-1701. [STEP 2]
3. Ko CW, Singh S, Feuerstein JD, et al. AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. *Gastroenterology*. 2019;156(3):748-764. [STEP 5]
4. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol.* 2019;114(3):384-413. [STEP 5]

Does prophylactic zinc supplementation decrease the incidence or mortality of pneumonia in children?

EVIDENCE-BASED ANSWER

Zinc supplementation reduces pneumonia incidence and mortality in children between two months old and five years old from developing countries or locations where zinc deficiency is common (SOR: **A**, systematic reviews and meta-analyses of randomized controlled trials).

DOI 10.1097/EBP.0000000000001753

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

A 2021 systemic review and meta-analysis of randomized controlled trials (RCTs) evaluated the effect of zinc supplementation on various mortality outcomes in children less than 5 years old.[1] Seven trials (N=197,334) focused specifically on mortality from pneumonia and were performed in Bangladesh (2 trials), India (2 trials), South Africa, East Africa, and Nepal. In five of these trials, children received ≥10 mg/d of zinc supplementation, and in the other two trials, patients received <10 mg/d of zinc (range: 5–20 mg/d). In five trials, zinc was combined with iron, folate, and other vitamin preparations, and the controls were the same preparations without zinc. One trial used zinc plus antibiotic versus just the antibiotic, and one trial used zinc versus placebo. Three trials used a duration of <11 months of zinc supplementation, and four studies had supplementary duration of ≥11 months. In four trials, follow-up duration was less than one year (range: 2–46 weeks), and in the remaining three trials, follow-up duration was greater than one year (range: 1–3 years). The diagnostic criteria for pneumonia were not specified. The relative risk for death from pneumonia with zinc supplementation was 0.79 (95% CI, 0.64–0.98), with low heterogeneity observed among these studies (I^2=21%). Using the Cochrane Risk of Bias tool 2.0, two of the trials included were found to have some concern of bias, whereas the other five trials were determined to have low risk of bias.

A 2016 systematic review and meta-analysis of six RCTs (N=5,193) conducted in India (2 trials), South Africa (2 trials), Bangladesh, and Peru compared zinc supplementation verses placebo for prevention of pneumonia in children 2 to 59 months old.[2] Of note, two trials from the review above (N=1,713) were also included in this review. Controls were largely similar to those in the trials mentioned above. Only one trial used chest radiography for the diagnosis of pneumonia; the other trials relied on clinical findings and criteria. One trial exclusively studied children who were HIV positive and one used inclusion criteria of children with diarrhea for at least 14 days. Patients received 10 mg zinc daily except in one trial where patients received 35 mg zinc weekly. Supplements were administered for at least three months (up to 20 months), with the primary outcome of pneumonia incidence assessed over at least four weeks (complete ranges not documented). Zinc supplementation decreased the incidence of pneumonia by 13% (risk ratio 0.87; 95% CI, 0.81–0.94). Although heterogeneity was low (I^2=0%), the study quality based on the GRADE Working Group criteria was also noted to be "low."

The World Health Organization (WHO) created a 2008 evidence-based bulletin regarding zinc supplementation in

children less than 5 years old in developing countries who are at heightened risk of having an acute lower respiratory tract infection (ALRI).[3] Although the WHO acknowledged that no standard definition for ALRI was present, in their evidence review, inclusion criteria was at least one lower respiratory tract clinical finding consistent with ALRI (eg, tachypnea, difficulty breathing, intercostal retractions, or abnormal findings on auscultation such as bronchial breath sounds, crepitus, or crackles). The WHO concluded that zinc supplementation in zinc-deficient populations significantly decreased the incidence of ALRI. The WHO provided no "strength" or "grade" to their recommendation. EBP

Vinusiya Shanmugalingam, MD
Meagan Dineen, MD
Jasmine Vayalil, DO
Benjamin Oesterling, DO
Arnett Family Medicine Residency—Indiana University School of Medicine, Lafayette, IN

The corresponding author is Benjamin Oesterling, DO; boesterlin@iuhealth.org.
The authors declare no conflicts of interest.

References

1. Rouhani P, Kelishadi MR, Saneei P. Effect of zinc supplementation on mortality in under 5-year children: a systematic review and meta-analysis of randomized clinical trials. *Eur J Nutr.* 2022;61:37–54. [STEP 1]
2. Lassi ZS, Moin A, Bhutta ZA. Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months. *Cochrane Database Syst Rev.* 2016;12. CD005978. [STEP 1]
3. Graham SM, English M, Hazir T, Enarson P, Duke T. Challenges to improving case management of childhood pneumonia at health facilities in resource-limited settings. *Bull World Health Organ.* 2008;86:349–355. [STEP 5]

What is the best nonpharmacological intervention to maintain weight loss after bariatric surgery?

EVIDENCE-BASED ANSWER

For most measures, postoperative behavioral weight management effectively assists in maintaining weight loss after bariatric surgery (SOR: **A**, systematic reviews with meta-analyses of randomized controlled trials and controlled trials). Compliance with 12 months of regular follow-up interventions after bariatric surgery results in increased percent excess weight loss (SOR: **B**, systematic review and meta-analysis of prospective cohort studies).

DOI 10.1097/EBP.0000000000001754

A 2020 systematic review and meta-analysis[1] examined 36 randomized controlled trials (RCTs), quasi-randomized trials, or "controlled before and after studies" (N=2,919) that evaluated the effect of behavioral weight management versus control groups on body mass index (BMI) and weight change after bariatric surgery. Inclusion criteria required trials target improving weight in bariatric surgery patients through behavioral/weight-related psychosocial change, report BMI or gross weight preintervention and postintervention, and have a comparison group of wait list control, usual care, or no intervention. Interventions included physical activity, dietary counseling, psychosocial based, or a combination of the above interventions. Patients were predominately White (62%), female (79%), from the U.S. or Europe (83%), and had an average age of 43 years. Most patients were status post Roux-en Y gastric bypass (63%) and average postoperative follow-up was 18.1 months (range 1.5–48 months). Standardized mean differences (SMDs) were calculated using pooled results of two outcomes—final mean values and changes in mean values. Pooled estimations were completed following mixed-effects models for group comparisons with small, medium, and large effects correlated with SMDs of 0.20, 0.50, and 0.80, respectively. Raw differences in means for weight and BMI (kg and kg/m^2) were also calculated.

For patients who received behavioral weight management after bariatric surgery (20 studies, N=1,223), the SMD favored the intervention group (SMD, –0.41; 95% CI, –0.77 to –0.05) albeit with a very broad CI (crossing nearly the entire SMD spectrum from "no" or "small" to "large" effect sizes). The absolute mean difference in weight did not prove significant (–4.94 kg;

95% CI, –10 to 1.1 kg). Studies with outcomes that included BMI (17 studies, N=1,113) favored the intervention group (SMD, –0.6; 95% CI, –0.91 to –0.29). The difference in the mean BMI loss favored the intervention group as well (–2.55 kg/m^2; 95% CI, –3.6 to –1.4 kg/m^2). Each of these four findings was reported with considerable heterogeneity (I^2 range, 88%–99%). Harms of the studies were not discussed in the review.

An earlier 2013 systematic review and meta-analysis of five RCTs (N=326) compared standard post-bariatric surgery recommendations with increased behavioral management for the primary outcome of weight loss.[2] Three of the five trials (N=206) included in this study were also included in the preceding systematic review and meta-analysis. Adult patients (≥18 years old, 74% female, average BMI 48.46 kg/m^2) who had received any type of bariatric surgical procedure were evaluated over a 12-month period from start of the intervention period for percentage of excess weight loss. Three of the studies had postoperative behavioral interventions starting immediately, one at six months, and one at >36 months. Session lengths were ranged between 15 and 90 minutes between studies. Intervention periods lasted from 3 to 36 months, with intervals between sessions from three times per month to every other month. Each trial used at least two distinct session types with four using individual sessions, and two each using telephone sessions, group sessions, or engagement with written materials. Using a random effects model for percentage of weight loss in the intervention groups, the SMD was calculated to be 1.6 (95% CI, 0.8–2.4) yet with considerable heterogeneity (I^2=87%). Several limitations were noted with this review, including the lack of standard guidelines for behavioral management content, techniques, leadership, and timing of initiation and extent of follow-up.

A 2014 systematic review and meta-analysis of four prospective cohort studies (N=365) evaluated the influence of patient compliance with follow-up after bariatric surgery to percent of excess weight loss.[3] Adult patients with mean ages of 40 to 47 years old and baseline BMI range of 47 to 52 kg/m^2 were followed for 12 to 48 months postsurgery. The four studies compared the percent excess weight loss (EWL) between the group of patients deemed compliant with follow-up (attended the 12-month visit or >3 visits) and the patient group not compliant with follow-up (no 12-month visit or ≤3 visits). Meta-analysis of data using a random effects model showed an increase in percent EWL at 12 months postsurgery in patients who were compliant with follow-up (mean difference 6.4% EWL; 95% CI, 1.6–11%; I^2=32%). EBP

Jeffrey P Williams, DO
Travis Dams, MD
Aimebenomon Omoye Idahosa, MD
Tobias Rumschlag, MD
Arnett Family Medicine Residency—Indiana University School of Medicine, West Lafayette, IN

The corresponding author is Jeffrey P. Williams; jwilliams21@iuhealth.org.
The authors declare no conflict of interest.

References

1. Julien CA, Lavoie KL, Ribeiro PAB, et al. Behavioral weight management interventions in metabolic and bariatric surgery: a systematic review and meta-analysis investigating optimal delivery timing. *Obes Rev.* 2021;22:e13168. [STEP 1]
2. Rudolph A, Hilbert A. Post-operative behavioural management in bariatric surgery: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev.* 2013;14:292-302. [STEP 1]
3. Kim HJ, Madan A, Fenton-Lee D. Does patient compliance with follow-up influence weight loss after gastric bypass surgery? A systematic review and meta-analysis. *Obes Surg*. 2014;24:647-651. [STEP 3]

What is the best non-invasive test for detecting hepatocellular carcinoma in adults with chronic liver disease?

EVIDENCE-BASED ANSWER

Contrast-enhanced magnetic resonance imaging (MRI) has higher sensitivity detecting hepatocellular carcinoma than contrast computerized tomography for lesions >2 cm; however, the performance of both imaging modalities declines substantially for smaller lesions, and both modalities have only modest accuracy for a lesion <1 cm. Use of gadoxetic contrast may improve MRI sensitivity (SOR: **B**, based on 2 meta-analyses of case series and case reports).

DOI 10.1097/EBP.0000000000001886

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

A 2017 systematic review and meta-analysis of 33 case series and case–control studies (N=2,250) investigated the relative diagnostic performance of multiphasic, cross-sectional contrast computerized tomography (CT) compared with magnetic resonance imaging (MRI) performed with extracellular contrast or the hepatocellular contrast agent gadoxetate in adults with all-cause cirrhosis and suspected hepatocellular carcinoma (HCC).[1] Gold standard diagnostic criteria included biopsy with or without clinical and radiological follow-up. The analysis excluded studies of only one imaging modality, case reports, and studies with fewer than five patients. Pooled analysis of the remaining studies showed a higher sensitivity (19 studies, N=1,694, sensitivity 0.82 vs 0.66, *P*=.0003) and a lower negative likelihood ratio (19 studies, N=1,694, negative likelihood ratio 0.20 vs 0.37, *P*=.001) for MRI compared with CT. Positive likelihood ratios were similar for both modalities (positive likelihood ratio [LR+] 8.8 for MRI vs LR+ 8.1 for CT). No difference was noted in performance of the type of MRI contrast. MRI showed higher sensitivity for HCC lesions <1 cm compared with CT (0.69 vs 0.49, *P*=.049), but no difference was noted in specificity, negative likelihood ratio, positive likelihood ratio, or diagnostic odds ratio. No difference was noted between MRI and CT for diagnosis of hepatic lesions between 1 and 2 cm. Studies were deemed low to moderate quality because of possible publication bias, heterogeneity of population characteristics such as severity and cause of cirrhosis, degree of portal hypertension, and frequency of obesity, and inconsistent reference standards among the studies.

A 2015 systematic review and meta-analysis of 40 case series and case–control studies (N=3,624) investigated the diagnostic performance of multidetector CT compared with MRI for the diagnosis of suspected HCC in adult patients with chronic liver disease or focal liver lesions with uncertain malignant potential.[2] This study shared six of the 40 studies (N=455) with the 2017 reference. The reference standard was histopathologic examination of an explanted, resected, or biopsied liver lesion. Studies with <10 patients or those that used a reference standard based on nonindex imaging studies were excluded. In a pooled analysis of only head-to-head studies, MRI had greater sensitivity per lesion compared with CT for lesions with average size 2 cm (range, 0.9–4.6 cm) (11 studies, N=639, 80% vs 68%, *P*=.0023). No difference was noted between MRI and CT for lesions <2 cm in size. MRI using gadoxetic contrast had greater sensitivity than other forms of contrast (10 studies, N=861, 87% vs 74%, *P*=.03). The study was limited by inclusion of only a small number of studies where data were reported prospectively, which may have biased results toward increased diagnostic sensitivity. Patients with previously identified and suspected HCCs were included in the study, which may have increased pretest probability Significant heterogeneity was noted in patient characteristics and technical aspects of imaging. EBP

Joshua Smothers, MD
David Spadavecchia, MD
Tea Kostandinis, MD
University of Missouri-Columbia, Columbia, MO

The corresponding author is Joshua Smothers;
jsmothers@health.missouri.edu
The authors declare no conflicts of interest.

References

1. Roberts LR, Sirlin CB, Zaiem F, et al. Imaging for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. *Hepatology*. 2018;67(1):401-421. [STEP 2]
2. Lee YJ, Lee JM, Lee JS, et al. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging-a systematic review and meta-analysis. *Radiology*. 2015;275(1):97-109. [STEP 2]

Is evening primrose oil an effective treatment of mastalgia?

EVIDENCE-BASED ANSWER

Evening primrose oil (EPO) might be an effective treatment of mastalgia. EPO seems less effective than topical NSAIDs for complete pain relief (SOR: **B**, meta-analysis of randomized controlled trials [RCTs]). However, EPO may reduce mastalgia pain scores more effectively than paracetamol (SOR: **C**, single, large RCT and conflicting meta-analysis).

DOI 10.1097/EBP.0000000000001918

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 13 randomized controlled trials (RCTs; N=1,752) evaluated the efficacy of evening primrose oil (EPO) as a treatment of mastalgia.[1] Patients were of any age with no restriction on comorbidities, and those who had a history of taking EPO at least three months before the trials were excluded. EPO was compared with placebo, vitamin E, danazol, and topical NSAIDs (piroxicam gel or diclofenac gel). The range of doses for EPO given orally were 1 to 4 g per day, vitamin E doses were 400 to 1,200 IU per day, and danazol were 200 mg per day. Trials lasted between one and three months. The primary outcomes were severity of pain and response to treatment or the number of cases achieving clinical response measured by the Cardiff Breast Pain Score (grade 1 and 2 = effective response to treatment, grade 3 and 4 = not responding to treatment). Because of different scales used in the trials, pain scores were pooled together and reported as a standardized mean difference (SMD). After six months, EPO did not significantly reduce breast pain compared with placebo (5 trials, N=525; SMD –0.37; 95% CI, –0.76 to 0.03) and or vitamin E (3 trials, N=305; SMD –0.47; 95% CI, –1.07 to 0.14). No difference was noted when compared with danazol. A greater number of patients who achieved pain relief with EPO treatment were present compared with patients treated with vitamin E (1 trial, n=61; relative risk [RR] 2.3; 95% CI, 1.2–4.4) but less when compared with topical NSAIDs (2 trials, N=120; RR 0.60; 95% CI, 0.43–0.84). EPO did not increase the occurrence of adverse effects compared with placebo, topical NSAIDs, danazol, and vitamin E.

A 2020 RCT (n=1,126) examined the effectiveness of EPO compared with paracetamol in treatment of mastalgia.[2] Participants were both adolescent and adult females (mean age 42 years old) admitted to a single-center outpatient specialty clinic and diagnosed with mastodynia without specifying cyclical or noncyclical pain. Patients with known cancer, pregnancy/breastfeeding, and those taking anticoagulation or hormonal treatment were excluded. Patients were randomized into EPO orally (1,300 mg, twice a day for 6 weeks) or paracetamol orally (500 mg, twice a day for 2 weeks). Both treatment arms used a 0 to 10 pain visual analog scale (VAS) to assess therapeutic efficacy. This was measured at enrollment, at two weeks, and at six weeks of treatment. A VAS score of less than one at six weeks was accepted as a reduction in mastalgia. EPO treatment had significantly lower VAS scores than the paracetamol group at both the second week (1.1 vs 2.4; $P<.001$) and the sixth week (0.83 vs 2.1; $P<.001$). No differences in side effects were noted. EBP

Socorro Shelton, MD
Quincy Scott, DO
Zin Ko Oo, MD
Nikhil Patel, DO
Zubin Wala, MO
Southern Illinois University Family Medicine Residency Program, Carbondale, IL

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

References

1. Ahmad Adni LL, Norhayati MN, Mohd Rosli RR, Muhammad J. A systematic review and meta-analysis of the efficacy of evening primrose oil for mastalgia treatment. *Int J Environ Res Public Health*. 2021; 18(12):6295. [STEP 1]
2. Balci FL, Uras C, Feldman S. Clinical factors affecting the therapeutic efficacy of evening primrose oil on mastalgia. *Ann Surg Oncol*. 2020; 27(12):4844–4852. [STEP 2]

What pharmacologic interventions are effective for preventing upper gastrointestinal bleeding in patients admitted to intensive care units?

EVIDENCE-BASED ANSWER

Proton pump inhibitors (PPIs) are more effective than histamine-2 receptor antagonists (H2RAs) at preventing clinically important upper gastrointestinal bleeding in critically ill patients. H2RAs, antacids, and sucralfate are more effective than placebo (SOR: **A**, systematic review of randomized controlled trials). PPIs and H2RAs are recommended for stress ulcer prevention in critically ill patients with high risk of upper gastrointestinal bleeding (SOR: **C**, clinical practice guideline).

DOI 10.1097/EBP.0000000000001987

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

A 2018 systematic review of 107 randomized controlled trials (RCTs) investigated approximately 15,000 intensive care unit (ICU) patients receiving interventions to prevent clinically important upper gastrointestinal bleeding.[1] Patients were of any age and gender and admitted to ICUs for >48 hours. Those admitted for gastrointestinal bleeding were excluded. The interventions studied were histamine-2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs), prostaglandin analogues, anticholinergics, potassium-competitive acid blockers, antacids (systemic and nonsystemic), sucralfate, bismuth, and other (enteral nutrition, combination regimens, and placebo) at any dose or route. Each class of drug was compared with no prophylaxis or placebo and then against one another. The primary outcome was clinically important upper gastrointestinal bleeding. PPIs were significantly more effective in preventing upper gastrointestinal bleeding in ICU patients than H2RAs (18 trials, N=1,636; relative risk [RR] 2.90; 95% CI, 1.83–4.58). When compared with no prophylaxis or placebo, H2RAs (24 trials, N=2,149; RR 0.50; 95% CI, 0.36–0.70) and antacids (8 trials, N=774; RR 0.49; 95% CI, 0.25–0.99) reduced the risk of clinically significant upper gastrointestinal bleeding. Sucralfate reduced the risk of upper gastrointestinal bleeding compared with placebo or no prophylaxis (7 trials, N=598; RR 0.53; 95% CI, 0.32–0.88). Other interventions were not found to significantly reduce the risk of clinically significant upper gastrointestinal bleeding.

A 2020 evidence-based, updated clinical practice guideline from the *British Medical Journal* recommended the use of stress ulcer prophylaxis in ICU patients with >4% risk of clinically important bleeding (a weak recommendation, benefits outweigh harms for the majority).[2] Use of a PPI was recommended to reduce the risk of clinically important bleeding more than H2RAs (weak recommendation). The guideline advised against administering sucralfate because it did not reduce the risk of clinically important bleeding compared with placebo (a strong recommendation, benefits outweigh risks for almost all). EBP

Megan Ward, MD, MPH
Sharon George, MD
Noureen Abbas, MD
Adam Ross, MD
Cahaba-UAB Family Medicine Residency Program, Birmingham, AL

The corresponding author is Adam Ross; adam.ross@cahabamedicalcare.com.
The authors declare no conflicts of interest.

References

1. Toews I, George AT, Peter JV, et al. Interventions for preventing upper gastrointestinal bleeding in people admitted to intensive care units. *Cochrane Database Syst Rev*. 2018; 6: CD008687. [STEP 1]
2. Ye Z, Blaser AR, Lytvyn L, et al. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. *BMJ*. 2020; 368:l6722. [STEP 5]

Are there any patient-centered pre-procedural interventions to reduce pain associated with endometrial biopsy?

EVIDENCE-BASED ANSWER

Intrauterine and cervical anesthetic are effective interventions for pain relief during outpatient endometrial biopsy (OEB; SOR: **A**, 2 meta-analysis studies of randomized controlled trials [RCTs]). During OEB with hysteroscopy, local anesthetic spray can also be used to reduce pain (SOR: **A**, Cochrane meta-analysis of RCTs). Misoprostol is ineffective for pain control (SOR: **A**, meta-analysis of RCTs).

DOI 10.1097/EBP.0000000000001857

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

A 2020 meta-analysis of randomized controlled trials (RCTs; N=3,091) evaluated effectiveness of pain control including intrauterine lidocaine, intrauterine levobupivacaine, oral or vaginal misoprostol, and oral NSAIDs during outpatient endometrial biopsy (OEB).[1] All trials included both premenopausal and postmenopausal female patients undergoing OEB, typically for abnormal uterine bleeding. Most common reason for a patient to be excluded from a trial was for pregnancy, infection of the cervix or pelvic inflammatory disease, hypersensitivity or allergy to the anesthetics, cervical stenosis, or the patient being hypercoagulable. Interventions included topical anesthetics (benzocaine spray or lidocaine spray), intrauterine medications (lidocaine or levobupivacaine), and systemic medications (naproxen, ibuprofen, etoricoxib, and etodolac). Controls were placebo with normal saline intrauterine or normal saline spray. The primary outcome was a pain score measured with a 10-cm visual pain scale (VAS), with 10 being worst pain ever and 0 being no pain. Compared with placebo, 5 mL of 2% intrauterine lidocaine and 5 mL of 5% levobupivacaine significantly reduced pain during OEB (5 trials, N=661; mean difference [MD] –1.31; 95% CI, –2.70 to –0.09; I^2=92%). When results were stratified by low- versus high-pressure devices, pain reduction was found to be significant in the low-pressure group (3 trials, N=321; MD –2.22; 95% CI, –3.72 to –0.73; I^2=83%) but not in the high-pressure group (2 trials, N=340; MD –0.01; 95% CI, –2.66 to 2.64; I^2=94%). Reduction in pain was not sustained after the OEB (3 trials, N=500; MD –0.69; 95% CI, –2.19 to 0.82; I^2=96%). Compared with placebo, anesthetic cervical spray such as 20% benzocaine 60-mg spray to cervix or 10% lidocaine 40-mg spray had similar results with a significant reduction in pain during the procedure (4 trials, N=608; MD –0.96; 95% CI, –1.53 to –0.39; I^2=62%) but not after the procedure (3 trials, N=520; MD –0.50; 95% CI, –1.32 to 0.33; I^2=88%). Compared to placebo, oral NSAIDs (naproxen 500–550 mg, ibuprofen 600 mg, etoricoxib 120 mg or etodolac at 400 mg) were also found to have a significant reduction in pain during OEB (3 trials, N=120; MD -1.01; 95% CI -1.77 to -0.25; I^2=73%). Misoprostol 200 μg was not only found to have no reduction in pain but was also associated with increased side effects, including nausea, diarrhea, cramping, abdominal pain, and vaginal bleeding, when compared with other interventions (eg, intrauterine anesthetic, oral anesthetic, or cervical anesthetic).

A 2017 Cochrane meta-analysis of 32 RCTs (N=3,304) examined the effectiveness and safety of pharmacological interventions for pain relief during outpatient hysteroscopy, including for OEB.[2] Hysteroscopy was used in OEB; however, it was clearly noted in the review that OEB had potential of additional pain because of uterine contraction. None of the RCTs were included in the study discussed above. All trials included women at least 18 years old, although the mean age varied as trials were different in focus on premenopausal women, postmenopausal women, or both. Other demographics and inclusion/exclusion criteria for patients were not specifically reported. Interventions included local anesthetics, NSAIDs, and opioids, whereas the control group received placebo or no treatment. The anesthetics included 2 to 20 mL of 1% to 2% mepivacaine, 4 to 30 mL of 2% lignocaine, 8 mL of 2% lidocaine, and 10 mL of 1% prilocaine. The primary outcomes included pain scores using a 10-cm VAS. When using local anesthesia in the form of paracervical, intracervical,

transcervical, or intrauterine block, a significant reduction in pain score was noted compared with placebo during the procedure (10 trials, N=1,496; MD –0.29; 95% CI, –0.39 to –0.19; I^2=80%) and 30 minutes afterward (5 trials, N=545; MD –0.50; 95% CI, –0.67 to –0.33; I^2=43%). However, the effect was too minimal to reliably translate to clinical significance. Topical anesthesia did not reduce pain compared with placebo (2 trials, N=368; MD –0.32; 95% CI, –0.97 to 0.33; I^2=90%). Oral NSAIDs, including celecoxib 200 mg, diclofenac 50 mg, and ibuprofen 600 mg, and oral paracetamol 1,000 mg also did not reduce pain compared with placebo (3 trials, N=521; MD –0.18; 95% CI –0.35 to –0.00; I^2=81%). Oral tramadol 100 mg did reduce pain compared with placebo (1 trial, n=140; MD –0.76; 95% CI, –1.10 to –0.42), but no pain reduction was found with sublingual buprenorphine 0.2 mg (1 trial, n=164; MD 0.08; 95% CI, –0.22 to 0.39). EBP

Brittanie West, MD, FAAFP
Tani Berzins, MD
Katharine MacMillan, DO
United Hospital Center Family Medicine Residency, Bridgeport, WV

The corresponding author is Brittanie West, MD, FAAFP; brittanie.west@wvumedicine.org
The authors declare no conflicts of interest.

References

1. Charoenkwan K, Nantasupha C. Methods of pain control during endometrial biopsy: a systematic review and meta-analysis of randomized controlled trials. *J Obstet Gynaecol Res*. 2020; 46(1):9–30. [STEP 1]
2. Ahmad G, Saluja S, O'Flynn H, Sorrentino A, Leach D, Watson A. Pain relief for outpatient hysteroscopy. *Cochrane Database Syst Rev*. 2017; 10:CD007710. [STEP 1]

Are hypertonic saline nebulizer treatments effective for inpatient treatment of bronchiolitis?

EVIDENCE-BASED ANSWER

When compared with 0.9% nebulized saline (NS), nebulized hypertonic saline (NHS) may reduce the length of hospitalization for bronchiolitis in children younger than two years by half a day and provide a small improvement in clinical severity scores (SOR: B, meta-analysis of randomized controlled trials (RCTs) and individual RCT). No difference in symptom resolution with NHS is seen when compared with humified high-flow oxygen (SOR: C, small RCT). Three days of NHS may decrease time to symptom resolution by half a day when compared with a single day of NHS (SOR: C; small RCT).

DOI 10.1097/EBP.0000000000001906

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

A 2020 meta-analysis of 32 randomized controlled trials (RCTs) evaluated the efficacy of using nebulized hypertonic saline (NHS) versus 0.9% saline nebulizers (NS) in hospitalized children younger than two years of with bronchiolitis (N=4,186).[1] Treatment variations included concurrent use of bronchodilators, nebulized epinephrine, and steroids. NHS volume varied from 2 to 5 mL. Severity of respiratory distress was measured by Respiratory Distress Assessment Instrument (RDAI, scale range 0–24). The NHS group showed decreased respiratory distress scores (5 trials; N=1,369; mean difference [MD] –0.60; 95% CI, –0.95 to –0.26). Secondary outcomes included a half-day reduction in length of hospital stay (20 trials, N=2,055, MD –0.54 days; 95% CI, –0.86 to –0.23). There were no statistically significant differences in readmission rates or time of sleeping at night. Adverse events included cough, bronchospasm, desaturation, agitation, rhinorrhea, tachycardia, hoarse voice, vigorous crying, vomiting, and diarrhea. All adverse events resolved spontaneously, and all patients completed the trial. A key limitation was the use of nonblinded evaluators of respiratory distress.

A 2017 meta-analysis of 28 RCTs (N=4,195) compared the efficacy of NHS (3%, 5%, and 7%) with NS for infants younger than 24 months with acute bronchiolitis.[2]

The review included RCTs with four treatment comparisons: NHS versus NS, NHS plus bronchodilators versus NS, NHS plus bronchodilators versus NS plus bronchodilators, and NHS with or without bronchodilators versus standard supportive therapy. NHS treatment compared with NS reduced the length of hospital stay (17 trials; N=1,867; –0.41 days [10 h]; 95% CI –0.75 to –0.07). Eleven of 13 trials used the Wang clinical severity scale (CSS), comprising a score of 0 to 3 points for each of four clinical conditions (respiratory rate, wheezing, retractions, and general condition), higher scores correlating with worse clinical status. NHS reduced postinhalation CSS scores in days 1 to 3 of treatment (day 1: 9 trials; N=812; MD –0.77, 95% CI –1.2 to –0.36; day 2: 8 trials; N=603; MD –1.3, 95% CI –1.9 to –0.65; day 3: 7 trials; N=499; MD – -1.4, 95% CI –1.8 to –1.0). NHS reduced hospitalization rate by 14% (8 trials; N=1,723; RR 0.86, 95% CI 0.76–0.98). Adverse events (11 trials, N=1,265) were mild and all resolved spontaneously. The quality of evidence was rated low to moderate due to high heterogeneity and variability in NHS concentrations.

A 2020 two-hospital, nonblinded RCT examined the effect of NHS versus supportive care on the length of stay for moderate–severe bronchiolitis in 160 hospitalized patients between six weeks and two years of age.[3] All patients had a Wang CSS between 5 and 12. The intervention group received 4 mL of 3% NHS every six h. Standard therapy included nasal suction, water–electrolyte balance, and supplemental oxygen. There was no difference in the length of hospitalization (47 h vs 50.4, MD -2.8 h; 95% CI -11 to 16), duration of supplemental oxygen (29.5 h vs 31.1, MD -1.5 h; 95% CI –9.6 to 12), racemic epinephrine use (5 patients vs 9, $P=.3$), transfer to PICU (0 patients vs 5, $P=.1$), or readmission (2 patients vs 3, $P=.7$). The study did not correct for preceding duration of illness. Ten patients discontinued NHS early by parent request.

A 2014 RCT compared NHS with heated humidified high-flow oxygen in 75 hospitalized children younger than six months of age with bronchiolitis and a RDAI score of ≥4.[4] Exclusion criteria included prematurity, chronic lung disease, cystic fibrosis, congenital heart disease, neuromuscular disease, airway anomalies, immunodeficiency, and immediate intubation. The comparison group received continuous heated humidified high-flow oxygen through nasal cannula (6–8 lpm) and nebulized epinephrine 1:1,000 with 2-mL NS, whereas the intervention group received oxygen through nasal cannula (goal oxygen saturation between 92–96%), nebulized epinephrine, and 3% NHS every four h for three cycles. Compared with humified high-flow oxygen, NHS resulted in no change in Respiratory Assessment Change Score (RDAI +change in % respiratory rate) or length of stay. Limitations of the study included the ability of attending physicians to order additional nebulizer treatments, and randomization that was broken by eight patients transferred from NHS to high-flow nasal cannula.

A 2019 RCT compared one versus three days of NHS in 103 infants younger than 12 months hospitalized with bronchiolitis.[5] One group (HS1D) received one day of NHS treatment followed by two days of NS; the other group (HS3D) received three days of NHS. The HS3D group had higher mean improvement in Wang CCS scores (MD 0.71, 90% CI 0.1–1.3) and shorter time to clinical remission (2.3 vs 2.9 days, $P=.04$). No differences were identified in rates of nutritional support, supplemental oxygenation, intolerance of nebulizer therapy, transfer to pediatric ICU, or length of stay > 6 days. Limitations of the study included use of 90% CI and inequivalent baseline demographic characteristics. EBP

Jeremiah Kakes, MD
Mark Gideonsen, MD
Nadine Nixon, MD
Michael Fassl, MD
Taylor Feuling, MD
Wisconsin Northcentral GME Consortium, Eau Claire, WI

Mark Gideonsen, MD; mark.gideonsen@prevea.com
The authors declare no conflicts of interest.

References

1. Hsieh CW, Chen C, Su HC, Chen KH. Exploring the efficacy of using hypertonic saline for nebulizing treatment in children with bronchiolitis: a meta-analysis of randomized controlled trials. *BMC Pediatr.* 2020; 20(1):434. [STEP 1]
2. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev.* 2017; 12(12): CD006458. [STEP 1]
3. Jaquet-Pilloud R, Verga ME, Russo M, Gehri M, Pauchard JY. Nebulised hypertonic saline in moderate-to-severe bronchiolitis: a randomised clinical trial. *Arch Dis Child.* 2020; 105(3):236–240. [STEP 2]
4. Bueno Campana M, Olivares Ortiz J, Notario Munoz C, et al. High flow therapy versus hypertonic saline in bronchiolitis:

randomised controlled trial. *Arch Dis Child.* 2014; 99(6): 511–515. [STEP 2]

5. Beal G, Barbier C, Thoret S, et al. Nebulized hypertonic saline 3% for 1 versus 3 days in hospitalized bronchiolitis: a blinded non-inferiority randomized controlled trial. *BMC Pediatr.* 2019; 19(1):417. [STEP 3]

Does the integration of behavioral health services in a primary care practice lead to improved outcomes in patients with PTSD?

EVIDENCE-BASED ANSWER

Yes. Integrated group therapy in primary care is associated with a 10% to 38% improvement in posttraumatic stress disorder (PTSD) symptoms (SOR: **B**, systematic review of randomized controlled trials [RCTs] and pre–post cohort trials). Telemedicine-based collaborative care can reduce PTSD symptom scores by 6% to 8% over usual care (SOR: **B**, single RCT), and Prolonged Exposure for Primary Care (PE-PC) treatment may lead to significant PTSD symptom reduction in a majority of patients with a number needed to treat of 2.2 (SOR: **C**, single small RCT).

DOI 10.1097/EBP.0000000000001920

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

A 2022 systematic review of four studies (2 randomized controlled trials [RCTs], 2 pre–post interventional cohort studies; N=97) evaluated the effect of group trauma therapy for posttraumatic stress disorder (PTSD) in primary care settings.[1] Most studies highlighted an underrepresented population, including transgender patients, Black women with HIV, and low-income patients. Studied treatments included emotion regulation training, mindfulness training, and psychoeducation in primary care over four to 16 group sessions of 90 to 120 minutes each. Two studies included patients on a wait list as the control group, whereas the other two pilot studies did not have a control group. The primary outcome was reduction in PTSD symptoms as measured on a symptom scale, which varied across studies and included the PTSD checklist-Civilian Version (PCL-C, score 17–85, ≥45 consistent with PTSD), PTSD Checklist-5 (PCL-5, score 0–80, ≥33 consistent with PTSD), and the clinician-administered PTSD scale (CAPS, score 0–120, high values indicating more symptoms). All studies demonstrated significant improvement in PTSD symptoms after group trauma therapy in the primary care setting, with mean percent decreases in symptom scores ranging from 18% to 38% (see **TABLE**). Limitations included small sample size, lack of control group in two studies, brief follow-up periods of less than four months, and a heterogeneity in treatment techniques and number of sessions.

A 2017 multicenter RCT (N=265) examined the effectiveness of telemedicine outreach for PTSD compared with usual care in rural settings.[2] Researchers recruited patients (90% male, 64% White) from Department of Veteran Affairs (VA) community-based outpatient clinics who met criteria for PTSD by the CAP scale. Patients with current treatment of PTSD at a VA medical center or current diagnosis of schizophrenia, bipolar disorder, or substance dependence were excluded. The intervention group received 12 months of onsite outpatient provider care supported by off-site PTSD care teams that included nurse care managers, pharmacists, psychologists, and psychiatrists. The control group received usual care. The primary outcome was PTSD severity as measured by the Posttraumatic Diagnostic Scale (PDS; 0–51 scale, higher scores indicate more severe symptoms, ≥28 consistent with PTSD). Compared with those receiving usual care, patients receiving TOP had on average greater reduction in PDS scores by 8.8% at six months (–5.9 vs –1.4; $P=.002$) and 6.1% at 12 months (–4.9 vs –1.8; $P=.04$). Limitations included a high opt-out rate and use of the briefer-over-the-phone PDS scale to maximize follow-up rate in place of the face-to-face CAP scale, which is the reference standard for PTSD severity.

A 2017 RCT (N=67) examined the effectiveness of PE-PC for the treatment of PTSD.[3] Researchers recruited active-duty service members (75% male) with a score of 32 or higher on the PTSD Checklist-Stressor-Specific Version (PCL-S; 17–85 scale, measuring PTSD symptom severity, ≥32 consistent with functional impairment) and psychotropic medication stability for at least four weeks. Exclusion criteria included risk of suicide, severe traumatic brain injury, alcohol or other severe substance use disorder

TABLE. Studies of the efficacy of group trauma therapy for PTSD in primary care settings[1]

Study	Treatment efficacy					
	No. of sessions	No. of subjects	Assessment Tool	Mean point difference	Mean % change	*P*
2017 RCT	12	7	PCL-C	–9.7	–18	.05
2020 RCT	8	30	PCL-5	–20	–35	<.001
2008 Pre–post cohort study	16	32	CAPS	–25	–38	<.001
2016 Pre–post cohort study	4	28	PCL-5	–12	–26	.02

CAPS=Clinician-administered PTSD scale (score 0–120, higher values more symptomatic); PCL-5=PTSD Checklist-5 (score 0–80, ≥33 consistent with PTSD); PCL-C=PTSD checklist-Civilian Version (score 17–85, ≥45 consistent with PTSD); PTSD=posttraumatic stress disorder; RCT=randomized controlled trial.

requiring immediate treatment, and current trauma-focused behavioral treatment. The intervention group received PE-PC in four 30-minute primary care appointments focused on emotional processing and review of at-home journaling of past trauma. The control group received four 5- to 10-minute phone calls from a behavioral health provider. Primary outcomes included the percentage of patients with a 15% or greater reduction in PTSD symptoms based on the PCL-S. Patients were followed up to six months. PTSD patients who received PE-PC were more likely to have a significant reduction in symptoms than the control group (62% vs 17%, *P*=.02), with a number needed to treat of 2.2. The study was limited to an active-duty military population with 85% of participants serving in the Air Force, whose trauma exposure may differ from those in ground combat roles. EBP

Angelina Cerimele, DO
Tiana Ibarra Yamamoto, DO
Kyle Walsh, MD
Savannah Wilkinson, DO
Jeremy A. Ginoza, DO
Skagit Regional Health Family Medicine Residency, Mount Vernon, WA

The corresponding author is Jeremy Ginoza; jginoza@skagitregionalhealth.org
The authors declare no conflicts of interest.

References

1. Schleyer W, Zona K, Quigley D, Spottswood M. Group therapy in primary care settings for the treatment of posttraumatic stress disorder: a systematic literature review. *Gen Hosp Psychiatry*. 2022; 77:1–10. [STEP 1]
2. Fortney JC, Pyne JM, Kimbrell TA, et al. Telemedicine-based collaborative care for posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry*. 2015; 72(1):58–67. [STEP 2]
3. Cigrang JA, Rauch SA, Mintz J, et al. Moving effective treatment for posttraumatic stress disorder to primary care: a randomized controlled trial with active duty military. *Families, Syst Health*. 2017; 35:450–462. [STEP 2]

Do ketogenic diets help pediatric patients with ADHD?

EVIDENCE-BASED ANSWER

A ketogenic diet probably does not improve attention deficit and hyperactivity disorder in pediatric patients (SOR: **C**, single, randomized, open-label controlled trial and clinical practice guideline).

DOI 10.1097/EBP.0000000000001954

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

A 2016 randomized controlled trial (RCT) (n=50) evaluated the effectiveness of a ketogenic diet on mood and behavior in children ages one to 18 years old with intractable epilepsy—defined as continuing to have seizures despite

being tried on two or more antiepileptic drugs.[1] This trial included as part of its focus attention deficit and hyperactivity disorder (ADHD). Eligible patients and their parents were referred by their attending physician to a single epilepsy specialty center in the Netherlands for consideration for inclusion in this trial. Researchers excluded patients with diabetes, fatty acid oxidation disorders, hypertriglyceridemia, severe liver disease, and many other comorbidities. The intervention group (n=28) received a ketogenic diet, and the controls (n=22) were treated with care as usual with both groups continuing their antiepileptic drugs, as previously prescribed. Mood, behavior, and neuropsychological assessments were performed at baseline, before randomization (1 month following baseline assessment), and after the four-month study period. Two behavioral assessments, the Strength and Difficulties Questionnaire (SDQ) and the Social Emotional Questionnaire (SEV) were used. The SDQ uses 20 questions with five questions covering each of four domains, one of which is "hyperactivity/inattention." A parent, teacher, or self-report is performed with each question receiving zero, one, or two points. Lower scores correlate with fewer behavioral problems. Similarly, the SEV is a 72-item questionnaire, which assesses four domains of social and emotional deficits, including "attention deficit and hyperactivity disorders" with lower scores equating to fewer behavioral problems. For the hyperactivity domain questions on the SDQ, baseline ketogenic diet and control scores were 6.1 and 6.5, respectively. The endpoint ketogenic diet and control scores were 4.8 and 4.9. The difference was reported as "not significant" based on a *P* value threshold of <0.05 for both the baseline and endpoint score differences. On the "attention deficit and hyperactivity disorders" domain questions on the SEV, baseline ketogenic diet and control scores were 29.9 and 28.7, respectively, compared with endpoint ketogenic diet and control scores of 26.6 and 25.2. These differences were again reported as "not significant" based upon a *P* value significance threshold of <0.05. Limitations to the trial included a 16% dropout rate, difficulty assessing adherence to a ketogenic diet, and limited generalizability to a population without intractable epilepsy.

Th American Academy of Pediatrics' 2019 clinical practice guideline covered a multitude of facets regarding the diagnosis and treatment of children with the diagnosis of ADHD. Regarding dietary modification, they stated that there was "too little evidence to recommend them or (they) have little or no benefit." EBP

Ann Payne-Johnson, MD, MS
Robert Perkins, MD, MPH
Phat Tran, MD
Timberly Wilson, MD, MS
Tyler Millo, DO
University of South Alabama Family Medicine Residency Program, Mobile, AL

The corresponding author is Ann Payne-Johnson, apjohnson@health.southalabama.edu
The authors declare no conflicts of interest.

Reference

1. Ijff DM, Postulart D, Lambrechts DAJE, et al. Cognitive and behavioral impact of the ketogenic diet in children and adolescents with refractory epilepsy: a randomized controlled trial. *Epilepsy Behav*. 2016; 60:153–157. [STEP 2]

Does starting a GLP-1 agonist in adults with prediabetes provide benefits over usual treatment?

EVIDENCE-BASED ANSWER

Liraglutide, a glucagon-like peptide (GLP)-1 agonist, may delay the onset of diabetes mellitus type 2 (DM-2) with a number needed to treat (NNT) of 22 when compared with placebo (SOR: **B**, large randomized controlled trial [RCT]); however, exenatide may not delay DM-2 (SOR: **C**, single small RCT). Patients given GLP-1 agonists (compared with placebo) have a higher rate of reversion to euglycemia (NNT=2; SOR: **B**, systematic review and meta-analysis of RCTs with limitations). However, the American Diabetes Association recommends that clinicians consider metformin as pharmacotherapy to prevent or delay DM-2 given its long history of safety data (SOR: **C**, consensus-based guideline).

DOI 10.1097/EBP.0000000000001885

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

A 2017 systematic review identified four randomized controlled trials (RCTs; N=2,507) of at least 12 weeks of duration evaluating the efficacy of glucagon-like peptide (GLP)-1 agonists for the prevention or delay of diabetes mellitus type 2 (DM-2) in at-risk adults.[1] Patients were predominantly female (range 63%–85%) with a mean age between 47 and 59 years old. The risk for DM-2 included any combination of impaired glucose tolerance, impaired fasting blood glucose, intermediate hyperglycemia (per the American Diabetes Association [ADA] or the World Health Organization [WHO] criteria), or HbA1c ≥5.7%. GLP-1 inhibitors included liraglutide 1.8 mg daily, liraglutide 3 mg daily, or exenatide 10 μg BID and were compared with placebo or metformin. Patients were followed for 14 to 172 weeks. The incidence of DM-2 was a primary outcome and a measure of glucose control was a secondary outcome. The authors summarized individual studies because they were not able to pool data for meta-analyses. One trial (n=2,210) found that 1.8% of patients given liraglutide 3 mg daily progressed to DM-2 compared with 6.2% of patients in the placebo arm after 160 weeks (risk ratio [RR] 0.28; 95% CI, 0.18–0.45). After discontinuing liraglutide for 12 weeks, five additional patients in the treatment arm had developed DM-2 compared with one patient in the placebo arm (hazard ratio 0.34; 95% CI, 0.22–0.53). However, another trial (n=33) found no significant difference in progression to DM-2 in patients given exenatide 10 μg BID versus placebo (11.8% vs 6.2%; RR 1.9; 95% CI, 0.19–18.8). Liraglutide 3 mg daily for 160 weeks yielded lower fasting plasma glucose levels compared with placebo (1 RCT, n=2,210; mean difference [MD] –0.42 mmol/L [–7.6 mg/dL]; 95% CI, –0.48 to –0.36 mmol/L). Similarly, patients given liraglutide 1.8 mg daily for 14 weeks had lower fasting plasma glucose levels compared with placebo (1 RCT, n=51; MD –0.6 mmol/L [–10.8 mg/dL]; 95% CI, –0.82 to –0.38 mmol/L). However, fasting plasma glucose levels were not significantly different comparing exenatide 10 μg BID with metformin 1,000 mg BID after three months (1 RCT, n=50; MD 0.0 mmol/L [0 mg/dL]; 95% CI, –0.31 to 0.31 mmol/L). Most trials did not report adverse events. The trials had unclear or considerable risk of bias in one or more domains and were of very low-quality evidence.

A 2022 systematic review and network meta-analysis of 47 RCTs (N=26,460) compared the efficacy of various interventions for reversing prediabetes (defined by the ADA or the WHO criteria) in adults.[2] Of the 47 studies, two examined GLP-1 agonists as the primary intervention (N=1,488) and 35 (N=10,164) included control patients given placebo or no intervention. One RCT (n=1,472 intervention group patients and n=738 control group patients) was included in the previously mentioned systematic review.[1] Patients given GLP-1 agonists differed from those in the control group in mean age (50.5 vs 52.9 years old), gender (24% vs 44% male), and race/ethnicity (83% vs 20% White). GLP-1 agonists were either liraglutide 3 mg daily for up to 160 weeks (1 RCT, n=1,472) or exenatide 2 mg weekly (with dapagliflozin 10 mg per day) for up to 24 weeks (1 RCT, n=16). Both studies included lifestyle modification recommendation in all therapy groups. The primary outcome was the number of patients with prediabetes who had normal fasting blood glucose levels (by the ADA or the WHO criteria), oral glucose tolerance test blood glucose <140 mg/dL (7.8 mmol/L), or HbA1c <5.7% by the end of the study. Patients receiving GLP-1 agonists were more likely than control group

patients to achieve the primary outcome after a median follow-up of 1.7 years (68% vs 21%; RR 3.5; 95% CI, 1.7–7.4; NNT=2). No adverse effects were reported. The quality of studies included in the meta-analysis were graded as moderate, down-graded because of moderate heterogeneity (I^2=60%) and imprecision.

A 2023 evidence- and consensus-based guideline from the ADA on prevention or delay of DM-2 recommended referral to an intensive lifestyle behavior change program for overweight or obese adults at high risk for DM-2 (A-level recommendation based on clear or supportive evidence from well-conducted RCTs).[3] The ADA guideline noted that several medications used for weight loss, including GLP-1 agonists, showed a reduction in the incidence of diabetes in patients with prediabetes; however, the guideline recommended clinicians consider prescribing metformin to select patients, especially those 25 to 59 years old with a body mass index of ≥35 kg/m^2, a high fasting plasma glucose (eg, >110 mg/dL), a high HbA1c (eg, >6.0%), or a history of gestational diabetes (A-level recommendation). The ADA guideline observed that no medications were approved by the U.S. Food and Drug Administration for prevention of DM-2, but that metformin had the longest history of safety data among drug treatments to prevent diabetes (no recommendation level provided). EBP

Christian D. Hoag, DO
Tori Kornelsen, MB, BCh, BAO
Christy M. Weiland, PharmD, BCPS
Jennifer Cherry Bohannan, MD
East Pierce Family Medicine Residency Program, Puyallup, WA

The corresponding author is Jennifer Cherry Bohannan; jbohannan@multicare.org
The authors declare no conflicts of interest.

References

1. Hemmingsen B, Sonne DP, Metzendorf MI, Richter B. Dipeptidyl-peptidase (DPP)-4 inhibitors and glucagon-like peptide (GLP)-1 analogues for prevention or delay of type 2 diabetes mellitus and its associated complications in people at increased risk for the development of type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2017;5(5): CD012204. [STEP 1]
2. Galaviz KI, Weber MB, Suvada KBS, et al. Interventions for reversing prediabetes: a systematic review and meta-analysis. *Am J Prev Med.* 2022;62(4):614-625. [STEP 1]
3. ElSayed NA, Aleppo G, Aroda VR, et al. 3. Prevention or delay of type 2 diabetes and associated comorbidities: standards of care in diabetes-2023. *Diabetes Care*. 2023; 46(suppl 1):S41-S48. [STEP 5]