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EVIDENCE-BASED PRACTICE

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FPIN
Family Physicians Inquiries Network

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EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

STATEMENT OF PURPOSE

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

EDITORIAL POLICY

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DISCLOSURE

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Is HbA1c or two-step glucose tolerance testing preferable for early diabetes screening in pregnancy?

CASE STUDY

You are seeing a 28-year-old G1P0 at 9 weeks for her initial OB visit. She has a prepregnancy body mass index (BMI) of 32 kg/m^2 and her mother has type 2 diabetes mellitus. She is otherwise healthy. You plan to perform early diabetes screening and wonder if obtaining HbA1c would suffice compared with a two-step glucose tolerance test (GTT).

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EVIDENCE-BASED ANSWER

There are no randomized controlled trials (RCTs) comparing HbA1c directly with the two-step glucose tolerance test (GTT) for early diabetes screening in pregnancy. However, several cohort studies have demonstrated the ability of HbA1c to adequately predict the development of gestational diabetes later in pregnancy, although sensitivity and specificity vary based on cut-off used (SOR: **B**, meta-analysis and systematic reviews of RCTs and cohort studies). In patients with known risk factors for diabetes, HbA1c may be useful in early risk stratification but cannot replace the two-step GTT in early gestational diabetes screening. However, an HbA1c is easier to obtain and may be a better option when considering social factors such as transportation or time needed for testing. Even if the results of early testing are negative, gestational diabetes screening using a two-step GTT is still recommended at 24 to 28 weeks of gestation.

Evidence-based summary

A 2020 meta-analysis of 23 studies (N=16,921) investigated the accuracy of HbA1c to screen women for diabetes in early pregnancy.[1] However, the trimester of testing varied with only six studies (N=7,100) using an HbA1c as a first trimester screening. The pooled sensitivity and specificity were 93% (95% CI, 0.66–0.99) and 22% (95% CI, 0.05–0.62) with an optimal cut-off of 5.2% to exclude diabetes.[1] The positive and negative likelihood ratios for a first trimester HbA1c test to predict the onset of gestational diabetes by the second/third trimester was 1.18 (95% CI, 0.71–1.66) and 0.34 (95% CI, 0.00–1.08).[1] The false-negative rate was 7% at a 5.2% HbA1c cut-off (**Table 1**).[1]

A 2020 systematic review identified 10 cohort studies (N=16,254) evaluating the screening power of HbA1c for the development of GDM, and all identified a positive correlation.[2] The risk of developing GDM increased with HbA1c ≥5.7%.[2] Studies were evaluated based on the Newcastle–Ottawa scale and were found to be high quality with low risk of bias.[2] However, a consistent HbA1c cut-off was not used and varied from 4.5 to ≥6.0 and had varying screening power.[2] An HbA1c cut-off >5.7% or >5.9% had high specificity (95%−98.4%) but had low sensitivity (14.5%−21%).[2]

A 2020 retrospective cohort study of 243 pregnant patients evaluated HbA1c as a diagnostic test for early GDM compared with two-step testing.[3] Median HbA1c levels were higher among women with GDM versus those without GDM (5.8% vs 5.3%), and the optimal threshold was 5.6% (64% sensitivity and 84% specificity).[3]

TABLE 1. Early pregnancy HbA1c levels and accuracy in screening for diabetes in early pregnancy

Study	Type of study	Population size (n)	HbA1c cut-off (%)	Sensitivity (%)	Specificity (%)
Amaefule et al.[1]	Meta-analysis	7,100	>5.2	93	22
Kattini et al.[2]	Systemic review	16,254	>5.7 or >5.9	14.5–21	95–98.4
Battarbee et al.[3]	Retrospective cohort	243	≥5.6	64	84
Bozkurt et al.[4]	Prospective cohort	220	≥5.7	96	20
Valadan et al.[5]	Prospective cohort	700	>4.85 ≥5.45	92 55	33 97

TABLE 2. Criteria for pregnant patients at increased risk of diabetes requiring early screening.[8]

BMI >25 kg/m^2 (or >23 kg/m^2 in Asian Americans) plus one or more additional risk factors:
• Physical inactivity
• First-degree relative with diabetes
• High-risk race or ethnicity (e.g., African American, Latino, Native American, Asian American, and Pacific Islander)
• Have previously given birth to an infant weighing 4,000 g (approximately 9 lb) or more
• Previous gestational diabetes mellitus
• Hypertension (140/90 mmHg or on therapy for hypertension)
• High-density lipoprotein cholesterol level <35 mg/dL (0.90 mmol/L), a triglyceride level >250 mg/dL (2.82 mmol/L)
• Women with polycystic ovarian syndrome
• HbA1c ≥5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
• Other clinical conditions associated with insulin resistance (e.g., prepregnancy BMI >40 kg/m^2, acanthosis nigricans)
• History of cardiovascular disease

However, the study was limited by its small sample size and single study site.[3]

A 2020 prospective cohort study of 220 pregnant patients evaluated if early pregnancy HbA1c represented glucose intolerance as seen in the oral GTT.[4] Increased HbA1c ≥5.7% was associated with altered glucose dynamics and showed a higher fasting, mean, and maximum glucose concentrations compared with those with normal-range HbA1c.[4] Specificity for the HbA1c cut-off of 5.7% was high at 96% (95% CI, 0.91–0.98), although sensitivity was low at 20% (95% CI, 0.12–0.30).[4] The study was limited by small sample size and a single study site.[4]

A 2022 prospective cohort study of 700 women examined the utility of HbA1c in first trimester detection of GDM.[5] In pregnant women with GDM, the average HbA1c level was 5.45% compared with 4.96% in the women without GDM.[5] The sensitivity and specificity varied based on the HbA1c cut-off and was 92% and 33% for a cut-off of 4.85 and was 55% and 97% for a cut-off of 5.45.[5]

Recommendations from others

The International Association of Diabetes and Pregnancy Study Groups (IADPSG), the American Diabetes Association (ADA), and the American College of Obstetricians and Gynecologists (ACOG) recommend early pregnancy screening using oral glucose tolerance testing for individuals at increased risk of undiagnosed type 2 diabetes mellitus (**TABLE 2**).[6–8] A 2021 United States Preventive Services Task Force (USPSTF) guideline concluded that available evidence was insufficient to assess the balance of benefits and harms of screening asymptomatic pregnant patients before 24 weeks of gestation.[9]

CASE CONCLUSION

Given the patient's increased risk of diabetes based on elevated BMI and family history of type 2 DM, you decide to perform an early two-step GTT and add a HbA1c to her initial prenatal laboratories to help screen for pregestational DM and early GDM and to better understand her risk for developing diabetes later in pregnancy. EBP

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The authors declare no conflicts of interest.

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Can early AROM reduce time to delivery in patients undergoing cervical ripening at term?

Gomez Slagle HB, Fonge YN, Caplan R, Pfeuti CK, Sciscione AC, Hoffman MK. Early vs expectant artificial rupture of membranes following Foley catheter ripening: a randomized controlled trial. Am J Obstet Gynecol. 2022; 226(5):724.e1-724.e9. doi:10.1016/j.ajog.2021.11.1368

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A randomized, unblinded clinical trial of 160 pregnant patients compared early amniotomy with expectant management after cervical ripening using misoprostol with a 30 cc Foley bulb. Early amniotomy was defined as artificial rupture of membranes (AROM) within one hour of Foley catheter expulsion or removal. Patients were at term, had a singleton pregnancy, were over 17 years old, and were undergoing induction of labor. A power analysis using a four-hour difference in labor time indicated a need for 160 patients assuming a 10% dropout and crossover rate. Randomization, including by parity, achieved well matched cohorts. Median times to delivery were 11.1 hours with early AROM; interquartile range (IQR), 6.25 to 17.1 versus 19.8 hours; IQR, 13.2 to 26.2; $P<.001$, without early AROM. No difference was observed in cesarean delivery rates, and no significant difference was seen in maternal or neonatal outcomes, including the use of interventions such as amnioinfusion and epidural. Limitations included a single medical center setting, use of both misoprostol and Foley bulb, and lack of blinding.

Methods

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

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

Bottom line: The study demonstrates significantly reduced time to delivery for term singleton pregnant patients, nulliparous or multiparous, undergoing misoprostol plus Foley bulb induction of labor using artificial rupture of membranes within one hour of Foley catheter bulb expulsion versus expectant management after expulsion. No differences were observed in maternal or neonatal outcomes.

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

Home BP Monitoring for At-risk Pregnant Patients

Tucker KL, Mort S, Yu LM, et al. Effect of Self-monitoring of Blood Pressure on Diagnosis of Hypertension During Higher-Risk Pregnancy: The BUMP 1 Randomized Clinical Trial [published correction appears in JAMA. 2022 Jul 12; 328(2):217]. JAMA. 2022; 327(17):1656-1665. doi:10.1001/jama.2022.4712

DOI 10.1097/EBP.0000000000001985

This randomized, controlled, nonblinded trial evaluated whether preeclampsia can be detected early in at-risk pregnant patients with self-monitoring of blood pressure. There were 2,441 patients recruited from 15 practices in England and randomized into the intervention group (n=1,223) versus usual care only (n=1,218). Researchers enrolled pregnant patients with 16 to 24 weeks of gestation with one or more risk factors for preeclampsia: age 40 years old or greater, >10 years from prior pregnancy, family history of preeclampsia, history of preeclampsia or gestational hypertension, BMI 30 kg/m^2 or greater, chronic kidney disease, twin gestation, prepregnancy diabetes, or autoimmune disease. Patients with preexisting hypertension were excluded. There were no significant differences

between the groups at randomization. The intervention consisted of home monitoring of blood pressure three times per week with two readings at each measurement, and the second measurement submitted through an app. Readings ≥140 systolic or ≥90 diastolic triggered a third reading and instruction to contact their physician. Patients were followed from 20 weeks of gestation through 12-week postpartum. The primary outcome was earlier detection of hypertension or diagnosis of preeclampsia, gestational hypertension, or prescription of antihypertensive medication. The dropout rate for the intervention group was 4.3% and for the usual care group was 3.5%. There was no significant difference in the primary outcome of time to the development of hypertension with 104.3 versus 106.2 days between the intervention group versus control group, respectively, and a mean difference of –1.6 days (95% CI, –8.1 to 4.9, $P=.64$).

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 "hypertension, pregnancy induced/diagnosis" [MeSH Major Topic] AND "home blood pressure monitoring" to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: This randomized controlled trial on home blood pressure monitoring to detect gestational hypertension in at-risk patients did not decrease the time to diagnosis of gestational hypertension. The USPSTF recommends screening for hypertension in pregnancy but gives no recommendations specifically addressing home monitoring. Prior data do support home blood pressure monitoring in patients with established gestational hypertension (to reduce the frequency of antenatal visits or need for hospitalization).

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Endometriosis and fibroids may predispose to adverse pregnancy outcomes

Farland LV, Stern JE, Liu CL, et al. Pregnancy outcomes among women with endometriosis and fibroids: registry linkage study in Massachusetts. *Am J Obstet Gynecol*. 2022; 226(6):829.e1-829.e14. doi:10.1016/j.ajog.2021.12.268.

DOI 10.1097/EBP.0000000000002073

This cohort study aimed to determine the prevalence of adverse maternal and neonatal outcomes in 91,825 deliveries of women 18 years old and older with endometriosis or fibroids. Researchers excluded mothers with Medicaid insurance and also assessed whether patients had medical care related to infertility. The primary outcomes included rates of maternal events (preeclampsia, eclampsia, cesarean delivery, gestational diabetes, and placental abnormalities) and infant events (small for gestational age, low birth weight, prematurity, and prolonged neonatal hospital stay), as well as neonatal conditions.

Of the deliveries, 1,560 (1.7%) women had endometriosis, 4,212 (4.6%) had fibroids, and 73,868 women had neither. Women with endometriosis had greater risk for hypertensive disorders (RR 1.17, 95% CI, 1.03–1.33), cesarean delivery (RR 1.22, 95% CI, 1.15–1.29), and placental abnormalities (RR 1.65, 95% CI 1.33–2.06), as well as greater risk for low birthweight infants (RR 1.23, 95% CI, 1.07–1.42) and preterm birth (RR 1.24, 95% CI, 1.09–1.41). Other maternal outcomes or pregnancy adverse outcomes did not remain statistically significant in stratified fertility subanalysis. Women with fibroids had greater risk for cesarean delivery (RR 1.17, 95% CI, 1.13–1.21), placental abnormalities (RR 1.38, 95% CI, 1.19–1.60), and preterm birth (RR 1.17, 95% CI 1.07–1.29).

While these results suggest increased risk for patients with endometriosis and fibroids, risk was lower in stratified analysis for fertility history, and the overall low relative risks are not clinically meaningful. Limitations included a smaller-than-expected prevalence of these conditions in comparison with expected population prevalence, and the sample was restricted to women who achieved live birth. Medicaid

patients were also excluded, and the patient population was majority Caucasian, making it less generalizable. Confounders such as tobacco use and other substance use that could have contributed to maternal and neonatal outcomes were also not accounted for.

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	No	Medical care setting	No
Valid	Yes	Implementable	No
Change in practice	No	Clinically meaningful	No

Bottom line: Whether endometriosis or fibroids contribute to clinically meaningful adverse maternal and neonatal outcomes remains unknown.

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Is pharmacogenomic-guided antidepressant treatment beneficial in the management of adults with major depressive disorder?

EVIDENCE-BASED ANSWER

Compared with patients receiving unguided therapy, adults with major depressive disorder receiving pharmacogenomic-guided antidepressant therapy are 41% more likely to achieve remission of depressive symptoms (SOR: **B**, meta-analysis of low-quality, randomized, control trials). In patients initially prescribed medications less favorable according to pharmacogenomic testing, 12% will experience some improvement in depressive symptoms, 12% will obtain a partial treatment response, and 13% will obtain full remission when switched to medications considered more favorable according to pharmacogenomic testing (SOR: **B**, single-blinded, randomized, control trial).

DOI 10.1097/EBP.0000000000001912

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

A 2022 systematic review and meta-analysis of 13 prospective, controlled, clinical trials (N=4,767) evaluated the effect of pharmacogenomic testing on the achievement of clinical remission of major depressive disorder (MDD).[1] Particularly relevant to pharmacogenetic studies, the majority of the patient population were females aged 40 to 50 years of European ancestry. Of the included studies, all but two exclusively enrolled participants with a primary diagnosis of MDD. Ten of the 13 trials used single-blinded (patient) or double-blinded (patient and rater) randomized controlled trial (RCT) design, and the remaining three used a controlled open-label design. The primary outcome measured was remission in depression as defined by the following: Hamilton Depression Rating Scale-17 (score ≤7), Clinical Global Impression Scale (score ≤2), or Patient Health Questionnaire (score ≤5). Summative risk ratios compared remission rates between pharmacogenomic-guided versus unguided treatment groups. Primary endpoints measurements varied between the studies, ranging from 8 weeks to 24 weeks, with 9 of the 13 studies measured endpoints at 8 weeks. Specific pharmacogenetic tests varied between the studies, but all included CYP2C19 and CYP2D6. Although pooled analysis of three open-label trials did not favor pharmacogenomic-guided therapy, pooled analysis of RCTs (10 trials, N=2,614, relative risk [RR] 1.5, 95% CI, 1.1–1.9) and all trials (RR 1.4, 95% CI, 1.2–1.7) favored pharmacogenomic-guided therapy for the remission of depression. Analysis of variables that could potentially impact the effect of pharmacogenomic-guided therapy on remission rates revealed that patients with greater number of prior medication trials (*Z score* 2.23, *P*=.026) or those who were more severely depressed (*Z score* 2.10, *P*=.036) derived greater benefit from pharmacogenomic-guided therapy. Variation in clinical recommendations and algorithms by different pharmacogenetic testing laboratories may have influenced clinician behavior.

A 2019 randomized control trial (N=1,398) evaluated the effect of pharmacogenomic-guided therapy in patients with MDD.[2] The trial included patients (mean age, 47.5 years, 71% were female, 81% white) diagnosed with MDD with inadequate response to at least one prior antidepressant, and mean HAM-D17 score at baseline of 21. Outcomes measured were symptom improvement, partial treatment response, and full remission of depression at week eight. Symptom improvement was defined as a decrease in HAM-D17 score less than 50%; partial treatment response was defined as greater than or equal to 50% decrease in HAM-D17 score; full remission was defined as a HAM-D17 score of less than or equal to seven. Patients were randomized to usual treatment or pharmacogenomics-guided intervention in which clinicians had access to pharmacogenomic test reports to inform medication selection. Pharmacogenomic-guided treatment achieved higher rates of partial treatment response (26% vs 20%, *P*=.013) and full remission (15% vs 10%, *P*=.007) but no better rates of symptom improvement (27% vs 24%, *P*=.1). Patients taking less favorable medications based on pharmacogenetic testing who switched to more favorable medications experienced greater symptom improvement (34% vs 21%, *P*=.002),

as well as partial treatment response (29% vs 17%, $P=.04$) and full remission (22% vs 8.5%, $P=.007$), compared with those who continued to take less favorable medications. Similarly, patients who switched to more favorable medications were less likely to experience side effects compared with those who remained on less favorable medications (6.5% vs 17%, $P=.045$). Study limitations included the lack of blinding of the treating physicians and the possible confounding effects of polypharmacy. EBP

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Childhood adversity impact on morbidity and mortality, an often forgotten risk factor

Association of Childhood Adversity With Morbidity and Mortality in US Adults

Grummitt LR, Kreski NT, Kim SG, Platt J, Keyes KM, McLaughlin KA. Association of Childhood Adversity With Morbidity and Mortality in US Adults: A Systematic Review. *JAMA Pediatr*. 2021 Dec 1; 175(12): 1269-1278. DOI 10.1097/EBP.0000000000002036

KEY TAKEAWAY: Childhood adversity is a significant contributor to morbidity and mortality in the United States

STUDY DESIGN: Systematic Review

LEVEL OF EVIDENCE: Step 2

BACKGROUND:
Childhood adversity affects around 50% of US children and is an important determinant of physical and mental health. Childhood adversity is associated with increased risk for numerous disease states but the degree to which childhood adversity contributes to premature mortality as a preventable driver of illness and death had not been studied.

PATIENTS: US population
INTERVENTION: Exposure to childhood adversity
CONTROL: No exposure
OUTCOME: Annual mortality

METHODS BRIEF DESCRIPTION:
- 12 forms of childhood adversity were identified for study including parental death, parental divorce, other parent loss, parent psychopathology, parent substance use, parent criminal behavior, family violence, physical abuse, sexual abuse, emotional abuse, neglect, and economic adversity.
- 19 meta-analyses of cohort studies with 20,654,832 participants were identified as eligible for review.
- The population attributable fraction (PAF) was applied to the number of annual deaths associated with each cause of death to estimate the number of deaths attributable to childhood adversity.
- All PAF ranges were reported from the lower and highest bounds of the 95% CI.

INTERVENTION (# IN THE GROUP): 439,072
COMPARISON (# IN THE GROUP): 2,415,766

FOLLOW UP PERIOD: Not available

RESULTS:
Primary Outcome
- Approximately 439,072 US deaths (15% of total US deaths in 2019) are annually attributable to childhood adversity through associations with leading causes of death in the United States:
  - Suicide (4+ Childhood Adversities (CAs), PAF range 0.384-0.783)
  - Cancer (4+ CAs, PAF range 0.075–0.162)
  - Heart disease (2+ CAs, PAF range 0.082–0.119)
  - Chronic lower respiratory disease (2+ CAs, PAF range 0.075–0.169)

Secondary Outcome
- Childhood adversity was associated with millions of cases of unhealthy behaviors and disease markers, including:
  - 22 million cases of sexually transmitted infections (4+ CAs, PAF range 0.180–0.495)
  - 19 million cases of elevated inflammation (4+ CAs, PAF range 0.145–0.204)
  - 21 million cases of illicit drug use (1+ CAs, PAF range 0.133–0.292)
  - More than 10 million cases of smoking (1+ CAs, PAF range, 0.052–0.144)

LIMITATIONS:
- Prevalence data was collected between 2001 and 2004 and therefore does not reflect any prevalence trends since that time.
- ORs were used to approximate the RRs for the PAF formula when RRs were not available.
- The meta-analyses differed somewhat in the specific childhood adversity criteria used. EBP

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Treatment of anal dysplasia prevents anal cancer

Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer

Palefsky JM, Lee JY, Jay N, et al. Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer. N England Journal of Medicine. 2022;386: 2273-2282. DOI 10.1097/EBP.0000000000002010

KEY TAKEAWAY: Treatment of high-grade anal dysplasia reduces the risk of progression to anal cancer in patients living with HIV.

STUDY DESIGN: Randomized control trial

LEVEL OF EVIDENCE: STEP 2

BACKGROUND: People living with HIV have high rates of anal cancer, believed to be related to HPV infection causing high-grade squamous intraepithelial lesions (HSIL). There is significant interest in whether screening for dysplasia may prevent anal cancer, analogous to the well-established screening program for cervical cancer. However, to date, there have been no prospective studies evaluating whether treatment of anal dysplasia reduces progression to anal cancer.

PATIENTS: Patients 35 years old and older living with HIV who have anal HSIL
INTERVENTION: Treatment of HSIL
COMPARISON: Active monitoring of HSIL (usual care)

OUTCOME: Incidence of anal cancer
SECONDARY OUTCOME: Adverse events

METHODS:
- This study recruited patients at 25 sites across the United States.
- Inclusion criteria: HIV infection, 35 years old and older, with biopsy-confirmed anal HSIL
- Exclusion criteria: history of anal cancer or anal cancer diagnosed at screening
- Patients were predominantly male (80%), had HIV for a median of 17 years, and with undetectable viral load (82–84%).
- Eligible patients were randomly assigned in a 1:1 ratio to either the treatment or control group.
- The treatment group had immediate treatment with the goal to eradicate all HSIL; the method of treatment was determined per clinician and patient preference but could include office-based ablation, ablation or excision under anesthesia, or topical fluorouracil or imiquimod.
  - Patients returned every six months for high-resolution anoscopy with further treatment of any recurrent lesions.
- The control group underwent HRA every six months with repeat biopsies of any visible lesions to confirm continued HSIL without progression to cancer.
- In both groups, lesions suspicious for anal cancer at any time were biopsied, and if positive, patients were immediately referred for therapy.
- Statistical analysis was based on time-to-event for progression to anal cancer (log-rank test)

INTERVENTION (# IN THE GROUP): 2,237
COMPARISON (# IN THE GROUP): 2,222

FOLLOW UP PERIOD: Median follow-up 25.8 months

RESULTS:
Primary Outcome
- HSIL treatment resulted in a 57% lower rate of progression of invasive anal cancer compared with active monitoring (173 per 100,000 person-years vs 402 per 100,000 person-years, respectively; 95% CI, 6–80).
- Cumulative incidence of progression to anal cancer at 48 months:
  - 0.9% in the treatment group
  - 1.8% in the control group

Secondary Outcome
- Seven trial-related serious adverse events were reported in the treatment group including skin ulceration, anal abscess or infection, and pain, compared with 1 serious adverse event in the control group (infection or abscess due to biopsy).

LIMITATIONS:
- The control group had a higher proportion of ever-smokers (61%) compared with the treatment group (56.9%), and smoking is likely to be an independent predictor of progression to anal cancer.
- Screening using anal Pap smears is not yet well-established in the community.
- The intervention studied is not available in many areas because few clinicians are trained in high-resolution anoscopy.

EBP

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Does treatment with daily antihistamines decrease the severity of interstitial cystitis symptoms?

EVIDENCE-BASED ANSWER

No. Antihistamines including cimetidine and hydroxyzine do not improve symptoms from bladder pain syndrome/interstitial cystitis (BPS/IC) (SOR: B; meta-analysis of 2 low-quality randomized control trials [RCTs]). Despite biopsies of bladder wall in BPS/IC showing greater histamine receptor expression, there is no correlation between expression of histamine receptors and response to antihistamines (SOR: C; bench research).

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

A 2020 network meta-analysis (81 RTCs; N=4,674) compared the effects of various interventions for treating people with symptoms of bladder pain syndrome (BPS).[1] There were 65 different active treatments including conservative, pharmacological, and surgical options. Two trials used in the meta-analysis included antihistamine use. The first study (London, 2001) included 36 patients diagnosed with painful bladder disease (PBD) based on a criterion of clinical history, cystoscopy examination with petechial hemorrhage, and bladder biopsy histology with chronic inflammatory infiltrates. Patients were given oral cimetidine 400 mg or placebo orally BID for three months. Patients were evaluated with a urinary symptom questionnaire and a cystoscopy with biopsy before and after the treatment. The symptoms questionnaire evaluated frequency, urgency, suprapubic pain, nocturia, and dysuria with scores from 0 to 5 according to severity with maximum score 35. The symptom score decreased from 19.7 to 11.9 in the cimetidine group, compared with 19.4 to 18.7 in the placebo group ($P<.05$). Histology examination of bladder biopsies showed no significant changes in the two groups, before or after treatment. The second was a 4-arm RCT (Raritan, New Jersey, 2003) that evaluated the safety and efficacy of oral pentosan polysulfate sodium (PPS), hydroxyzine, the combination of PPS and hydroxyzine, and placebo in 121 patients with interstitial cystitis (IC).[2] All patients were 18 years old and older with at least moderate symptoms of urinary frequency (at least 11 times daily) and pain/discomfort (at least 4 on a 0–9 Likert scale) for at least 24 weeks and confirmed diagnosis of IC using cystoscopy and hydrodistension. Patients were treated and followed for 24 weeks using PPS 1100 mg capsules three times a day (TID) with hydroxyzine titrated from 10 mg to 50 mg daily over three weeks and with placebo. A 7-point centered scale was used and included markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, and markedly improved. Patients who reported either of the latter two categories were defined as treatment responders. The study showed no significant difference in the global response rate between hydroxyzine and no hydroxyzine treatment. A higher, but nonsignificant, response was observed in patients receiving any PPS treatment compared with no PPS (34% vs 18%, $P=.064$), with the highest response rate in the PPS and hydroxyzine combination (40% vs 28% in PPS alone vs 23% in hydroxyzine alone). Limitations of the study included a low rate of recruitment (30:1 contact to randomization ratio), and post hoc power analysis indicated a need for 1,000 patients to detect differences in patients receiving hydroxyzine, indicating an overall low to negligible efficacy. The meta-analysis showed neither cimetidine nor PPS with hydroxyzine combination improved cure/improvement rates, reduced pain, reduced ICSI (Interstitial Cystitis Symptom Index) score, or reduced ICPI (Interstitial Cystitis Problem Index) score. Limitations of the meta-analysis included great uncertainty around estimates of effects and low number of studies with antihistamines.

A 2019 retrospective cohort study explored the differential expression of histamine receptors and their responsiveness to antihistamines in the bladder wall tissues of patients with BPS/IC versus control.[2] The study population included 69 patients admitted to the Beijing Chaoyang Hospital from 2005 to 2009 with BPS/IC based on National Institute of Diabetes and Digestive and Kidney Diseases guidelines. The control included 10 patients without BPS/IC but receiving surgical treatment for stress urinary incontinence. A follow-up study included patients who received antihistamines (amitriptyline or cimetidine) and were divided into responders

TABLE. Antihistamine receptor expression in bladder tissue of patient with bladder pain syndrome/interstitial cystitis (BPS/IC) and controls[2]

Antihistamine Receptor	Receptor Mean Density BPS/IC* Group	Receptor Mean Density Controls	*P*-value
1 (H1R)	0.14	0.04	< 0.001
2 (H2R)	0.09	0.06	0.03
3 (H3R)	0.11	0.08	0.008
4 (H4R)	0.10	0.06	0.05

Mean Density=integral optical density (IOD)/area.

(n=38) with improved pain, urgency, and frequency versus non responders (n=22). The outcome measured was the quantity of four histamine receptors as detected by antibodies on biopsies of bladder tissue. The result showed greater antihistamine receptor levels in patients with BPS/IC compared with control (see **TABLE**). Some patients with BPS/IC who received amitriptyline or cimetidine were evaluated for improvement of clinical symptoms (pain, urgency, frequency) and classified as responders or nonresponders. They examined the histamine receptor expression between the responders and nonresponders and did not see a statistical difference. The limitation of this study was that the treatment group included both amitriptyline and cimetidine; therefore, differentiating effect of one agent over the other was not possible. In addition, the primary outcomes were disease-oriented and not patient-oriented. EBP

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Is tadalafil effective in treating lower urinary tract symptoms in males with benign prostatic hyperplasia?

EVIDENCE-BASED ANSWER

For male patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH), tadalafil is well tolerated and moderately effective in improving symptoms and quality of life with no significant difference in serious adverse events when compared with placebo (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Tadalafil is superior to tamsulosin when LUTS from BPH is associated with erectile dysfunction (ED), with similar improvement in LUTS and greater improvement in ED (SOR: **A,** systematic review RCTs). Tadalafil should be discussed as a treatment option for men with symptomatic BPH (SOR: **C**, expert opinion).

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

A 2021 meta-analysis of 15 randomized controlled trials (RCTs) (N=9,525) evaluated the efficacy and clinical safety of tadalafil for LUTS associated with benign prostatic hyperplasia (BPH).[1] Trials included adult male patients with BPH treated with either tadalafil 5 mg once daily or placebo for 12 weeks. The primary outcome was the change in total International Prostate Symptoms Score (IPSS; scoring range 0–35), IPSS storage (or

irritative) subscore (range 0–15), IPSS voiding (or obstructive) subscore (range 0–20), BPH Impact Index (BII; range 0–13), IPSS quality of life (QoL; range 0–6), adverse events (AEs), serious adverse events (SAEs), maximum flow rate (Qmax), and postvoid residual volume (PVR) over 12 weeks measured at baseline and after the treatment period. Compared with placebo, tadalafil treatment improved the total IPSS (15 trials, n=9,525 mean difference [MD] –1.97; 95% CI, –2.2 to –1.7), the IPSS voiding (15 trials, N=9,525, MD –1.3; 95% CI, –1.5 to –1.1), storage subscores (MD –0.70; 95% CI, –0.82 to –0.58), IPSS QoL (14 trials, N=9,423, MD –0.29; 95% CI, –0.35 to –0.22), and BII (8 trials, N=3,682, MD –0.58; 95% CI, –0.76 to –0.50) but not the Qmax or PVR. Tadalafil and placebo were similar in the incidence of SAEs, although AEs were higher in the tadalafil group (RR 1.2; 95% CI, 1.2–1.4). Tadalafil monotherapy showed a higher incidence of headache, dyspepsia, and back pain. Limitations included incomplete outcome data in four studies that may have led to attrition bias.

A 2020 meta-analysis of seven RCTs (N=1,601) evaluated the effect of tadalafil compared with tamsulosin in the treatment of LUTS from BPH.[2] The trials included adult male patients treated with tadalafil 5 mg or tamsulosin 0.2 or 0.4 mg once daily over 12 weeks. The primary outcomes were similar to the previous meta-analysis, with the addition of the International Index of Erectile Function (IIEF). The IIEF is a 15-item questionnaire for the assessment of erectile function across five domains (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction). Total IPSS, voiding or storage subscores, QoL, or PVR scores did not differ between the treatment groups, whereas IIEF did. Compared with tamsulosin, tadalafil improved IIEF scores (2 trials, N=208, weighted mean difference [WMD] 5.0; 95% CI, 3.8–6.3). Limitations included heterogeneity between the aging men with LUTS treated by tadalafil and tamsulosin.

A 2022 prospective RCT (N=92) compared effectiveness of tadalafil with tamsulosin in male patients 40 years or older with symptomatic BPH.[3] The trial excluded patients with any of the following medical conditions: hematuria, chronic kidney disease, bilateral hydroureteronephrosis, bladder calculi, bladder diverticula, or who were on alpha-blockers. Patients were randomly assigned to receive either tamsulosin 0.4 mg PO daily or tadalafil 5 mg PO daily. Primary outcomes included changes in PVR, Qmax IPSS, and Sexual Health Inventory for Men (SHIM). The SHIM consists of five questions asked to each patient, and each question carried a score of one to five (total score 22–25 = no erectile dysfunction [ED], 17–21 = mild ED, 12–16 = mild to moderate ED, 8–11—moderate ED, and 5–7 = severe ED). Patients were assessed at baseline, three months, and six months post treatment. Compared with tamsulosin, tadalafil resulted in similar improvements in Qmax, PVRU, and IPSS, but a greater improvement in SHIM (3 months mean 16 vs 22, $P<.005$; 6 months mean 16 vs 22, $P<.001$).

The 2021 American Urological Association (AUA) practice guidelines for the management of LUTS from BPH discussed the use of tadalafil based on 10 RCTs.[4] The guidelines stated that for patients with LUTS arising from BPH irrespective of comorbid ED, 5 mg of daily tadalafil should be discussed as a treatment option (moderate recommendation; evidence level: grade B). EBP

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Is there an association between post-acute sequelae of SARS-CoV-2 Infection (PASC) and spike protein levels?

EVIDENCE-BASED ANSWER

A likely association between the presence of spike protein levels and postacute sequelae of SARS-CoV-2 (PASC) or long COVID up to 12 months after a positive COVID diagnosis is present (SOR: **C**, small retrospective cohort study). Spike protein levels are significantly higher in PASC patients with or without neuropsychiatric manifestations than healthy controls (SOR: **C,** small cohort study).

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A 2022 retrospective cohort study (n=63) examined spike protein levels in patients who were infected with SARS-CoV-2 or developed postacute sequelae of SARS-CoV-2 (PASC).[1] Patients were adults between 26 and 83 years old with 64% female and 84% White at Ragon Institute of Mass General Hospital. After PCR confirmation of COVID infection, blood samples were collected from PASC (n=37) and non-PASC (n=26) groups serially for up to 12 months. Non-PASC controls were selected from the electronic medical records. Protein levels were detected if they met limit of detection (LOD) calculated as the background average enzyme per bead plus three times the standard deviation. The primary outcome was spike protein antigen levels versus time after diagnosis with PASC and control subjects. Secondary outcomes classified antigen detection according to associated organ system and related symptoms after infection with the same LOD calculated above. Greater than 70% of patients with ongoing PASC symptoms had LOD antigen levels, whereas 23% of non-PASC subjects had LOD antigen levels (*P* value not reported). No harm was reported from sample collection. Limitations included having a small sample size with unmatched cohort controls from self-referred or physician referred subjects and lack of pediatric patients despite the presence of PASC in children.

A 2022 cohort study (n=58) in San Francisco examined patients' plasma for any association between neural-derived protein profiles and neuropsychiatric symptoms after SARS-CoV-2 infection.[2] Patients had a mean age of 43 years old with 72% female. Inclusion criteria were a positive COVID test result from a nasal or throat swab sample. Exclusion criteria included transfusion dependent anemia, HIV/AIDS, and other known immunodeficiency. Patients were classified as five groups: being healthy control (n=12), COVID-19 without PASC (n=8), PASC without neuropsychiatric manifestations (NP, n=15), PASC with NP (n=15), and PASC with severe NP (n=8). NP was classified using a composite measure of patient health questionnaire (PHQ)-8 for depression (except suicidal ideation), generalized anxiety disorder (GAD)-7, and EuroQol EQ-5D for quality of life that evaluated 20 psychiatric symptoms. Patients with seven symptoms or fewer were classified as NP, and patients with eight or more symptoms were classified as severe NP. Serum plasma was collected from healthy controls in 2015 before the pandemic or COVID vaccine while the other patients' samples were taken between April

TABLE. Association between plasma neuron-derived extracellular vesicle spike protein, postacute sequelae of COVID-19, and neuropsychiatric manifestations in source patients and controls

Comparison groups	Plasma neuron-derived extracellular vesicle spike protein in pg/mL	Significance
PASC w/NP (n=15) vs Control (n=12)	1,128 vs 197	*P*<.001
PASC w/severe NP (n=8) vs Control (n=12)	994 vs 197	*P*<.001
PASC w/o NP (n=15) vs Control (n=12)	839 vs 197	*P*<.05
COVID w/o PASC (n=8) vs Control (n=12)	628 vs 197	*P*<.001

24, 2020, and February 11, 2021. The primary outcome consisted of quantification of plasma neuron-derived extracellular vesicle (NDEV) protein levels. All comparator groups had significantly higher levels of NDEV spike S1 than the control (**TABLE**). No side effects were reported. This study was limited by the small sample size and single plasma samples. EBP

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Do higher maternal choline levels correlate with improved neonatal outcomes in pregnant women with respiratory infections?

EVIDENCE-BASED ANSWER

In mothers with a history of respiratory infection, higher maternal serum choline levels (≥7.5 μM/L) are associated with higher infant self-regulation at three months old (SOR: **C**, observational studies). Among mothers with common maternal viral infections, higher choline levels are also associated with higher self-regulation, specifically attention duration (SOR: **C,** small cohort study).

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

A 2019 cross-sectional study (n=201) examined the association between choline levels and maternal infections on infant behavior at three months old.[1] Patients were predominantly White mothers (80%) with a mean age of 30 years old. Pregnant patients were selected from a public hospital prenatal clinic before 16 weeks' gestation. Pregnancies with fetal anomaly, severe intrauterine growth restriction, or corticosteroid use were excluded. Maternal serum choline was measured at 16 weeks' gestation. Mothers underwent in-person review of systems for symptoms of infection at 16, 22, 28, and 34 weeks' gestation. Infections reported were genitourinary, respiratory, or gastrointestinal in nature. The outcomes included infant behavior at three months old, including regulation as measured by the infant behavior questionnaire–revised short form (IBQ-R). Ninety-one infant behaviors were rated on Likert scales ranging from 1 (never) to 7 (always) which were then averaged into 14 scales of infant behavior and temperament. These scales were then grouped into 3 domains of regulation, negativity, and surgency. Higher scores in the regulation domain indicated higher levels of duration of attention, enjoyment of quiet play, cuddliness and engagement with parents, and ability to soothe. A significant, positive association was observed in mothers with infections between higher gestational choline levels and development of self-regulation

among infants at three months old (β=0.29, *P*=.03). However, no significant association was found among infants of mothers with no infection.

A 2020 cohort study (n=96) examined a subset of the 2019 study population to evaluate the outcomes of offspring exposed in utero to respiratory illnesses and the relationship to maternal choline levels.[2] Patients included 77% White mothers with a mean age of 30 years old at 16 weeks' gestation. As per the US Food and Drug Administration dietary recommendations, sufficient choline levels were defined as ≥7.5 μM/L. Pregnancies with fetal anomaly, severe intrauterine growth restriction, or corticosteroid use were excluded. At 16 weeks' gestation, maternal serum choline levels were drawn. Patients were asked through self-ratings about symptoms of illness with a respiratory virus within the previous six weeks. The neonatal outcomes included infant behaviors at three months as measured by the IBQ-R. At three months, compared with infants of infected mothers with insufficient choline levels, infants of infected mothers with sufficient choline levels had significantly increased scores in the regulation domain (5.2 vs 4.6, *P*=.002) than infants of mothers with insufficient choline. Specifically, a significant difference was observed in the subdomain of attention duration (range 0–7) between the two groups (sufficient choline 4.2 vs insufficient choline 2.6, *P*=.006). However, among uninfected mothers at three months, choline levels were not associated with regulatory or attention duration. This study was limited by the single center, small sample size, and predominately White mothers. In addition, the IBQ-R regulation domain did not have a minimum threshold that was considered abnormal, so results should be cautiously interpreted. EBP

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What is the best type of oral solution for adults to consume during exercise to decrease dehydration effects?

EVIDENCE-BASED ANSWER

Hypotonic oral rehydration solutions (ORSs) may decrease plasma volume loss by up to 2% of total body volume compared with hypertonic solutions, isotonic solutions, or water (SOR: **C**, meta-analysis of crossover trials using disease-oriented outcomes). In addition, hypotonic ORSs containing glucose seem to decrease the susceptibility of cramping more than spring water alone (SOR: **C**, small crossover trial).

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

A 2021 meta-analysis of 28 randomized controlled trials (RCTs) with 226 patients assessed the effect of oral rehydration solution (ORS) concentration on dehydration during exercise.[1] Patients ranged from nonathlete healthy adults to elite athletes (mean age of 26 years, 93% male). The solutions studied were classified into one of three categories: hypertonic (>300 mOsmol/kg), hypotonic (<275 mOsmol/kg), isotonic (275–300 mOsm), and water from tap. All solutions were consumed orally at an ingestion rate of at least 1 mL/min. Studies were excluded if they used drinks containing protein or a one-time drink bolus. Patients exercised up to 180 minutes. Researchers chose delta plasma volume (ΔPV, the change in plasm volume before and after the intervention) as the primary outcome and a surrogate measure for dehydration. There was

minimal difference in ΔPV across the different ORS concentrations, although hypotonic fluid seemed to best minimize the decrease in ΔPV by 1% to 2% (hypertonic –7.4%; 90% CI, –8.5% to –6.3%; hypotonic –6.3%; 90% CI, –7.4% to –5.3%; isotonic –8.7%; 90% CI, –10.1% to –7.4%; water –7.5%; 90% CI, –8.5% to –6.4%). Limitations included the use of a non–patient-oriented outcome, a predominantly male population, and lack of standardization in how to measure ΔPV.

A 2021 randomized crossover study (n=10) assessed the effects of a formulated ORS on the susceptibility of muscle cramping during exercise (this study was not included in the above meta-analysis).[2] Patients were healthy men, 22 to 31 years old, who participated in moderate exercise or sports less than 300 minutes per week and were not prone to muscle cramps at baseline. Patients underwent two rounds of testing one week apart, with either ORS or spring water consumed at timed intervals during downhill running for 40 to 60 minutes in 35 to 36°C (95–97°F) weather. The ORS was a proprietary hypotonic solution containing glucose. Researchers weighed patients at regular intervals during exercise and administered a fluid volume corresponding to their body weight lost. After one week, each patient underwent the same testing protocol with the other solution. The primary outcome was the change in cramping susceptibility of the calf muscle, measured as cramp threshold frequency (TF). Researchers electrically stimulated the patients' dominant calf muscle with different electrical frequencies, measuring a camp TF by observation of visibly taut muscle combined with patient report of pain. Cramp TF was measured before, immediately after, 30 minutes after, and 65 minutes after exercise. Ingestion of the studied hypotonic ORS decreased susceptibility to cramping compared with spring water, with TF decreasing from 3.8 to 4.5 Hz for spring water and increasing from 6.5 to 13.6 Hz for ORS ($P<.05$). The ORS used in the study is not readily commercially available. EBP

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Which methods of contraceptive counseling result in the highest patient satisfaction when measured within 6 months of contraceptive counseling?

EVIDENCE-BASED ANSWER

Patients undergoing contraception counseling are more satisfied with interactive counseling methods such as motivational interviewing, a Facebook page, and a paper joint decision-making tool. Satisfaction is not improved by special provider training in counseling and is lower than usual counseling in less interactive methods like pamphlets, videos, and an informational mobile app (SOR: **B**, systematic review of limited-quality studies). Patients find an educational video and effectiveness chart more supportive of their contraceptive choice compared with a box of models (SOR: **B**, cross-sectional study). A printed computer-based decision aid tool is not more effective than a general reproductive health survey (SOR: **B**, randomized controlled trial).

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

A 2019 systematic review of 33 randomized controlled trials (RCTs), 14 uncontrolled pre–post studies, nine observational studies, and four quasi-experimental studies (N=111,236) evaluated the effect of different contraceptive counseling strategies on patient satisfaction.[1] Patients were reproductive-age women or couples from the World Health Organization (WHO) Americas region (29 of 61 studies) and the United States (22 of 61 studies). Counseling methods included digital decision-making tools (n=263), paper-based decision-making tools (n=1,048), provider training in counseling skills (n=4,895), provider training in antenatal counseling (n=28,068), or provider training in counseling post abortion (n=251). Head-to-head comparison of counseling strategies was not possible due to study heterogeneity. Patient satisfaction was higher with an interactive Facebook page, motivational interviewing, and an interactive WHO provider–patient paper decision-making tool when compared with usual counseling or pre–post scores. Noninteractive

TABLE. Satisfaction outcomes of various counseling methods compared with usual counseling[1]

Counseling Method	Study design	N	Outcome measured	Patient satisfaction
Interactive Facebook page with video, diagram, and games versus ACOG pamphlet	RCT	n=143	Median counseling satisfaction score (0–10; max=10)	Higher with Facebook page (median 10 vs 6, $P<.001$)
Noninteractive, informational mobile application vs health educator counseling	RCT	n=120	% "very satisfied" with counseling	Lower with noninteractive mobile application (57% vs 92%, $P=.001$)
Pamphlet vs usual counseling in family planning clinic	Quasi-experimental	n=600	% "will recommend clinic to friends"	No difference (97% vs 97%, $P=.05$)
Pamphlet vs usual counseling in antenatal patients	RCT	n=319	% "satisfied"	Lower with pamphlet (93% vs 99%, $P=.044$)
Informational videos for clients post abortion	RCT	n=191	Satisfaction score (max=5)	No difference (4.8 vs 4.7, $P=.82$)
Informational video vs usual counseling for antenatal clients	RCT	n=319	% "satisfied with counseling"	Lower with informational video (91% vs 99%, $P=.044$)
Motivational interviewing vs nonstandardized counseling for clients post abortion	RCT	n=60	% "satisfied with counseling"	Higher with motivational interviewing (92% vs 65%, $P=.04$)
Special provider training in contraceptive counseling skills vs no training	Quasi-experimental study	n=1,728	% satisfied with services	No difference (99% vs 98%, OR=1.5, $P=.05$)
	Quasi-experimental study	n=480	% would recommend clinic to friends	No difference (96% vs 95%, no P value reported)
	Nonrandomized control study	n=1,320	% satisfied with visit	No difference (94% vs 100%, $P=.01$)
	Uncontrolled pre–post study	n=516	% satisfied with overall services	No difference (91% vs. 93% $P=.05$)
	Uncontrolled pre–post study	n=27,622	% "satisfied" or "very satisfied" with counseling	No difference (80% vs 74%, no P value reported)
An interactive WHO provider–patient paper decision-making tool	Uncontrolled pre–post study	n=448	% satisfied % who would recommend service to others	Higher with WHO decision making tool (72% vs 99%, $P=.03$ and 56% vs 98%, $P=.05$, resp.)
Intensive antenatal counseling	RCT	n=127	% "client satisfaction"	No difference (92% vs 93%, $P=1.00$)

methods, such as pamphlets or a mobile app, had lower satisfaction scores than usual in person counseling (see **TABLE**). Harms of all counseling methods, versus usual practice, included provider time burden and upfront cost of digital tools, training, and client handouts. Limitations of the review included wide heterogeneity, lack of blinding and selection bias in nonrandomized studies, and lack of standardized satisfaction measures.

A 2021 cross-sectional study (n=658) on patients and health care providers in the intervention group of a cluster randomized trial measured satisfaction of structured contraceptive counseling compared with standard contraceptive counseling.[2] The structured contraceptive counseling included an educational video, key questions asked by a health care provider, an effectiveness chart, and a box of contraceptive models. Patients were older than 18 years (median age 24 years), sexually active, did not desire to conceive, and wished to use contraception as a means of pregnancy prevention. In a follow-up survey, patients found the educational video (67.4%) and chart (55.9%) more supportive of their contraceptive choice compared with a box of contraceptive models (51.3%). Limitations of the study included the educational video being only available in Swedish with English subtitles.

A 2020 RCT compared a printed computer-based contraceptive decision aid (n=161) with a general reproductive health survey (n=80) serving as the control for women seeking reversible contraception.[3] The primary outcome measure was decisional conflict, assessed pre and post visit, and measured with a validated 10-item Decisional Conflict Scale. The secondary outcomes included satisfaction with health providers' counseling measured with a 5-point scale (1 = "not satisfied" to 5 = "very satisfied") and contraceptive method choice. Patients were 18 to 45 years old, 57.7% White, 35.3% Black, and recruited from two academic gynecology clinics. Patients completed the decision aid or health survey before their appointment and the satisfaction survey after. There was no difference in contraceptive counseling satisfaction between the groups (P=.91, dataset unavailable). Limitations included unequal distribution of race between the two arms, nonblinding of the health care provider to which intervention the patient received, the possibility that provider counseling offset the benefit for the decision aid used, and risk of type II error. EBP

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The authors declare no conflicts of interest.

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Are corticosteroids useful in the treatment of rebound headache?

EVIDENCE-BASED ANSWER

No significant differences are observed in the outcomes between prednisone and placebo or prednisone and celecoxib in treatment of medication-overuse headache (SOR: **B**, systematic review of low-quality randomized controlled trials). The European Academy of Neurology 2020 guidelines provided no recommendations for prednisone use for withdrawal symptoms in medication-overuse headaches (no SOR given).

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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 16 randomized controlled trials (N=1,105) evaluated interventions for adults with medication overuse headache (MOH).[1] Of the 16 trials analyzed, three trials (N=198) evaluated the use of prednisone versus placebo and one trial (N=80) assessed prednisone versus celecoxib after medication withdrawal. The diagnosis of MOH was based on criteria of the International Classification of Headache Disorders (ICHD) definition. Patients included in the review were older than 16 years old, with women representing 82% of the studied population across the four steroid trials. All trials cited included a baseline period of approximately four weeks to assess potential participants for study qualification. In the studies' intervention phases, prednisone dosing ranged from 60 to 100 mg/day, with dosage reduction during the treatment period between the fifth and sixth days. Patient follow-up ensued between five days and eight weeks. Different outcome measures for headaches were reported using headache diaries (eg, number of headache days, headache intensity, headache improvement). No significant difference was observed in efficacy measures between the steroid and placebo groups in any of the studies. Owing to the heterogeneity between different trials, meta-analysis could not be performed. Using GRADE criteria, the overall quality of the evidence was deemed "low" to "very low."

In 2020, the European Academy of Neurology (EAN) published clinical guidelines for management of MOHs, including a specific recommendation on the use of medications for withdrawal symptoms.[2] The EAN also used the ICHD definition for MOH. The EAN performed a systematic review as part of their guideline development which included three trials (N=237) focusing on steroids, two of which were included in the preceding systematic review. The GRADE of each trial was determined to be "low" quality. The guideline authors determined that they could make no specific recommendation regarding steroid use for this indication. EBP

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In adult patients with asthma, does regular aerobic exercise improve asthma symptoms as compared with patients with asthma who do not regularly exercise?

EVIDENCE-BASED ANSWER

In adults with asthma, regular aerobic exercise has a small beneficial effect on asthma symptoms with a number needed to treat (NNT) for any improvement of four (SOR: **A**, meta-analysis of randomized controlled trial (RCTs), consistent with subsequent RCT).

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

A 2020 systematic review and meta-analysis (11 randomized controlled trial [RCTs], N=543) evaluated the effect of aerobic exercise training on asthma control.[1] Researchers studied adults (mean age 35 years old, 75% female) with a physician diagnosis of asthma, varying in severity from mild to severe. Interventions included various programs of aerobic exercise (ie, walking, jogging, cycling, swimming, etc) at least twice a week for 8 to 12 weeks. Comparison groups either underwent no intervention or received counseling on

breathing exercises. Outcomes included change in asthma control after the exercise program, measured with the Asthma Control Questionnaire (ACQ) or asthma-related quality of life (ARQoL) scale. Owing to measure heterogeneity, outcomes were analyzed across studies using standardized mean difference (SMD; results defined as: 0.2–0.5 small effect, 0.5–0.8 moderate effect, and >0.8 large effect). Aerobic exercise programs improved asthma control with a small effect (7 RCTs, N=359; SMD 0.48; 95% CI, 0.16–0.81). Limitations included the high heterogeneity of studies, specifically with variance in exercise intervention and outcome measures. Patient blinding was also impossible with exercise as the intervention.

A 2019 RCT (n=131) evaluated whether a 24-week exercise program could improve asthma control.[2] Researchers recruited adult patients (18–65 years old) diagnosed with mild-to-moderate asthma by a physician (based on the Finnish Guidelines for Asthma Management). Those with severe asthma, other major chronic disease (severe coronary disease, heart failure, severe musculoskeletal disorder, dementia, or chronic obstructive pulmonary disease), or individuals who already routinely exercised at least three times weekly were excluded. A trained nurse provided the intervention group a personalized exercise program including at least 30 minutes of aerobic exercise, along with strength training and stretching, three times per week for 24 weeks. The nurse saw patients at 12 weeks to modify the exercise program as needed and provide encouragement. The comparison group received no specific exercise guidance. The primary outcome was the proportion of patients with improvement in the Asthma Control Test (ACT), a standardized five-question survey of asthma symptoms (range of 5–25 points). In the intervention group, 62% of patients had an improved ACT score after the 24-week exercise program, whereas 39% of patients improved in the comparison group, an NNT for symptom improvement of 4 (risk difference 0.23; 95% CI, 0.027–0.44). Researchers did not quantify the degree of symptom improvement in the study. The study was conducted entirely in Finland, possibly affecting generalizability. EBP

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Does omega-3 fatty acid supplementation provide cardiovascular benefits?

EVIDENCE-BASED ANSWER

Probably not in most patients. For all patients except the highest cardiovascular risk, increasing eicosapentaenoic acid and docosahexaenoic acid has little or no effect on death and cardiovascular events (SOR: **B**, systematic review with varying interventions). However, for those patients with elevated triglycerides on statin therapy and other risks for cardiovascular disease, high-dose (1.86–2 g eicosapentaenoic acid) supplementation may be associated with decreases in cardiovascular death, sudden death, nonfatal myocardial infarction, and nonfatal stroke. (SOR: **B**, one systematic review and meta-analysis and one randomized controlled trial).

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

In 2020, a systematic review and meta-analysis of 86 randomized-controlled trials (RCTs; N=162,796) compared the efficacy of higher omega-3 fatty acids with a lower or usual intake of omega-3 fatty acids on all-cause mortality and cardiovascular diseases.[1] The review included trials of at least 12 months in patients older than 18 years old with and without existing cardiovascular disease. The supplementation of omega-3 fatty acids may have been in oil or capsule form or as foodstuffs provided and must have been oily fish or fish oils as a food, oil, made into a spreading fat or supplementing another food. Refined eicosapentaenoic acid

(EPA), docosahexaenoic acid, concentrated fish, or algal oils were also accepted. Increasing omega-3 fatty acid intake did not decrease all-cause mortality (45 RCTs; N=143,693; relative risk [RR] 0.97; 95% CI, 0.93–1.01) or cardiovascular events (43 RCTs; N=140,482; RR 0.96; 95% CI, 0.92–1.01) although it slightly reduced the risk of cardiovascular mortality (29 RCTs; N=117,837; RR 0.92; 95% CI, 0.86–0.99, number needed to treat [NNT]=258) and coronary heart disease events (32 RCTs; N=134,116; RR 0.91; 95% CI, 0.85–0.97; NNT=167) when compared with usual or lower intake. No significant harms were associated with higher omega-3 fatty acid intake. The systematic review was of moderate quality because of the high number of patients; but trial reliance on self-reporting was a key weakness.

A 2021 systematic review and meta-analysis of 17 double-blind RCTs (N=83,617) compared the efficacy of four doses of omega-3 oral supplements on reducing cardiovascular outcomes (all-cause mortality, cardiovascular [CV] mortality, sudden death, nonfatal myocardial infarction [MI], and stroke among adults).[2] The review only included studies with at least one year of follow-up (range 1–6.2 years). One study included healthy adults (14% with diabetes); all other studies included patients with a documented history of or high risk for CV disease. Median age at enrollment ranged from 49 to 70 years old. Interventions were examined within four groups according to EPA dose and subsequently analyzed across two groups, low dose (<1.68 g EPA) and high dose (1.8–6 g EPA). Control group patients took a placebo containing nonmarine oils or similar. No significant difference was observed in any CV outcomes for low-dose EPA supplementation. At the higher doses, statistically significant reductions were observed in a random effects analysis for cardiac death (6 trials; N=9,516; RR=0.78; 95% CI, 0.65–0.93; NNT=128), sudden death (3 trials; N=8,982; RR=0.67; 95% CI, 0.47–0.91; NNT=83), and stroke (3 trials, N=8,413; RR=0.73, 95% CI, 0.57–0.94; NNT=114). No significance was found using a more conservative trial sequential analysis, suggesting evidence of benefit is weak. Side effects were not discussed.

A multicenter, randomized, double-blinded, placebo-controlled study investigated cardiovascular risk reduction using icosapent ethyl (purified EPA) compared with controls in patients with hypertriglyceridemia.[3] The study included 8,179 patients older than 45 years old with cardiovascular disease (secondary prevention) or diabetes mellitus with risk factors (primary prevention) and a fasting triglyceride of 200 to 499 mg/dL on appropriate statin therapy. The study group received icosapent ethyl 2 g twice a day versus placebo received mineral oil capsules. The primary endpoint was a composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and unstable angina. Secondary endpoints were CV death, nonfatal MI, and nonfatal stroke. At five-year follow-up, a primary composite endpoint occurred in 17.2% of the treatment group and 22% of the placebo group (hazard ratio [HR] 0.75; 95% CI, 0.68–0.83; NNT=21). Secondary endpoints were also lower in the treatment group, with HR 0.75 (95% CI, 0.66–0.86) for CV death, 0.69 (95% CI, 0.58–0.81) for fatal or nonfatal myocardial infarction and 0.72 (95% CI, 0.55–0.93) for fatal or nonfatal stroke. Rates of adverse effects of icosapent ethyl versus placebo did not differ and included gastrointestinal events (33%, 35.1%), diarrhea (9%, 11.1%), and anemia (4.7, 5.8%). The manufacturer of icosapent ethyl sponsored the trial. EBP

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What are the most effective screening tools for adolescents at risk of suicide?

EVIDENCE-BASED ANSWER

The Ask Suicide-Screening Questions and the Computerized Adaptive Screen for Suicidal Youth instruments are effective screening tools for adolescents at risk for suicide (SOR: **B**, prospective cohort study).

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

A 2023 prospective, random series, multicenter cohort study (n=2,740) assessed the Ask Suicide-Screening Questions (ASQ) and the Computerized Adaptive Screen for Suicidal Youth (CASSY) instruments as to how they compare in predicting suicide attempts (SAs) among adolescents.[1] This study used a prediction model to assess outcomes, the primary outcome was SA, and the secondary outcome was suicide-related events (SRE). Adolescents 12 to 17 years old were recruited, and the study oversampled for those with psychiatric symptoms who visited the Emergency Department from July 24, 2017, through October 29, 2018. Researchers excluded patients who were in significant pain and those who did not complete the baseline evaluations, the CASSY or ASQ, or the three-month follow-up. Over half of the patients were girls (n=1,705, or 62%), and over half were White (n=1,608, or 59%). All patients completed a CASSY, an ASQ, and a three-month follow-up assessment. After statistical analysis, no significant differences were noted between the ASQ and the CASSY with respect to sensitivity (0.951 vs 0.945), specificity (0.59 vs 0.64), positive predictive value (0.13 vs 0.14), and negative predictive value (NPV; both 0.99). Area under the receiver operating characteristic curve findings were similar between all patients with physical symptoms; however, among patients with psychiatric symptoms, the CASSY performed better than the ASQ (0.72 vs 0.57, respectively). Some limitations to this study include the fact that it was primarily conducted in academic medical centers and that Black patients, those who presented with psychiatric symptoms, and those whose parents had a low socioeconomic status and were less educated experienced higher attrition rates.

A 2021 cross-sectional instrument validation study (n=551) assessed the validity of the ASQ, a 4-item screening instrument, comparing it with the Suicidal Ideation Questionnaire (SIQ) as the standard criterion measure, screening for frequency of suicidal ideation.[2] English-speaking patients from outpatient specialty diabetes, endocrinology, sports medicine, or orthopedic clinics and primary care clinics who were 10 to 21 years old (mean age 15 years old) were included. The data were obtained from two different children's hospitals, November 2015 through July 2017. Researchers excluded patients with psychological instability because of medical illness, non–English-speaking primary caretaker, and any disability, impairment, or disorder that rendered the patient unable to comprehend questions and communicate answers. Approximately 53% of the patients were female, and 40% were White. In a total of 335 outpatient specialty clinics, 180 primary care clinic participants completed the study interview before or after being seen by their provider. In specialty clinics, the ASQ showed a sensitivity of 100%, specificity of 91%, and NPV of 100%. The positive likelihood ration (+LR) was 11 and the negative likelihood ratio (–LR) was 0. In the primary care clinic, the ASQ showed a sensitivity of 100%, specificity of 88%, +LR of 8.3, and –LR of 0. Forty-five (13%) outpatient specialty clinic patients and 28 (16%) primary care clinic patients screened positive for suicide risk on the ASQ. The screen had substantial agreement with the SIQ for detecting suicide risk (area under receiver operator curve 0.94). Some limitations in this study included potential differences between the convenience sample and the general population of youth in nonemergency outpatient settings. In addition, there may have been survey fatigue because of repeatedly asking the participants about suicide ideation. EBP

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Are mindfulness-based interventions effective in the treatment of adult ADHD?

EVIDENCE-BASED ANSWER

Mindfulness-based interventions (MBI) that include meditation, psychoeducation, cognitive behavioral therapy (CBT), and group discussions in conjunction with standard treatment may improve symptoms and behaviors in adults with attention-deficit/hyperactivity disorder (ADHD) when compared with standard treatment alone, with a number needed to treat (NNT) of 4 (SOR: **B**; randomized controlled trial [RCT]). MBI may be equal to psychoeducation (PE) in treating adult ADHD symptoms and behaviors (SOR: **C**, small RCT).

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

A 2019 single-blinded RCT (n=120) of adults in the Netherlands with ADHD investigated the benefit of adding mindfulness-based cognitive behavioral therapy (MBCT) to usual treatment.[1] The patients had a mean age of 39 years old, and 53% were female; ADHD was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Researchers excluded patients with a current depressive disorder with psychotic symptoms or suicidality, current manic episode, borderline or antisocial personality disorder, substance dependence, autism spectrum disorder, tic disorder with vocal tics, learning difficulties or other cognitive impairments, and former participation in mindfulness-based workshops. The MBCT consisted of eight weekly two-and-a-half-hour sessions of meditation, psychoeducation, CBT, and group discussions as well as 30-minute guided mindfulness home exercises six days a week. Usual treatment included pharmacotherapy (in 54% of patients), psychoeducation/skills training (in 58%), or psychosocial therapy (in 55%). The primary outcome was change from baseline to eight weeks and eight months in the investigator-rated screening version of the Conners' Adult ADHD Rating Scale (CAARS-INV; range 0–198; where higher scores=greater ADHD symptoms). The CAARS-INV was scored by a clinician blinded to the intervention. MBCT added to usual treatment produced a greater reduction in CAARS-INV scores compared with usual treatment alone both at eight weeks (mean difference [MD] −3.4; 95% CI, −5.8 to −1.1) and at eight months (MD −3.6; 95% CI, −5.6 to −1.7). At eight weeks, the MBCT plus usual treatment arm had significantly better results in the number of patients who had improved (31% vs 5%; P=.001; NNT=4), had clinically significant symptom reduction of at least 30% (27% vs 4%; P=.001; NNT=4), or had symptom remission (21% vs 7%; P=.04; NNT=7) compared with usual treatment alone. No statistically significant difference was observed in the percentage of patients deteriorating between the two groups. No identifiable harms of the interventions were observed. This RCT was limited by a lack of data on the individuals excluded from participation and lack of assessment of the success of clinician blinding.

A 2018 RCT (n=81) evaluated the effectiveness of mindfulness awareness practices (MAP) compared with an active control of psychoeducation (PE) in patients with DSM-IV–diagnosed ADHD.[2] Patients were recruited from a behavioral health clinic at a German university and were on average 39.5 years old; 52% were female. The study excluded patients with schizophrenia, bipolar I, current substance dependence, autism, acute suicidality, self-injurious behavior, or neurologic disorders, as well as those on ADHD medications and anyone who had received psychotherapeutic treatment within three months of enrollment. Both interventions consisted of eight weekly two-and-a-half-hour sessions conducted by trained psychotherapists. MAP focused on attention to the present moment with an accepting mindset and with a constructive approach to dealing with negative thoughts, supplemented by daily sitting meditations and exercises in daily living. PE informed patients of the causes, symptoms, and treatment of ADHD and provided tools for organization and stress management. The primary outcome was the change in the subscale CAARS-INV scores from baseline to eight weeks and eight months. Both treatments improved CAARS-INV scores in all subscales at eight weeks (percent improvement ranged from 15% to 33%, depending on subscale; $P \leq .001$ when compared with baseline scores) and in two of eight subscales at eight months (percent improvement ranged from 8% to 30%, depending on subscale; $P \leq .05$ when compared with baseline scores). However, no significant differences were observed between treatment groups in any subscale. This

RCT was limited by the lack of a comparison with standard ADHD treatments such as pharmacotherapy. EBP

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What is the most effective and safest treatment of depression after CABG?

EVIDENCE-BASED ANSWER

Escitalopram and nonpharmacologic treatments including psychological interventions and comprehensive rehabilitation and intensive education seem to be effective for the treatment of depression in patients with coronary heart disease, including those post–coronary artery bypass graft (CABG; SOR: **B**, meta-analysis of randomized controlled trials [RCTs] and one RCT). Escitalopram is safe, not associated with a difference in morbidity and mortality in patients post-CABG, and may lead to improvement in cardiac outcomes in patients post–acute coronary syndrome (SOR: **B**, two RCTs).

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

A 2017 systematic review of 35 randomized studies (N=10,703) of patients with coronary heart disease assessed the effectiveness of psychological interventions (alone or with other rehabilitation) compared with usual care (including cardiac rehabilitation where available) on depression, total mortality, cardiac mortality, and cardiac morbidity.[1] The study populations consisted of patients after myocardial infarction (MI), after a revascularization procedure such as coronary artery bypass graft (CABG) or percutaneous intervention (PCI), and adults with angina or angiographically defined coronary artery disease (CAD). Psychological interventions had a small effect reducing patient-reported depression (19 trials, N=5,825, standardized mean difference [SMD] –0.27; 95% CI, –0.39 to –0.15); however, this was based on low-quality evidence. In addition, psychological interventions resulted in a 21% reduction in cardiac mortality (11 trials, N=4,792, risk ratio [RR] 0.79; 95% CI, 0.63–0.98). Psychological interventions did not change the rates of total mortality (23 trials, N=7,776, RR 0.90; 95% CI, 0.77–1.05), revascularization procedures (13 trials, N=6,822, RR 0.94; 95% CI, 0.81–1.11), or nonfatal MI (13 trials, N=7,845, RR 0.82; 95% CI, 0.64–1.05).

A 2019 randomized controlled trial (RCT, n=300) evaluated the effect of a comprehensive rehabilitation and intensive education (CRIE) program versus usual care (UC) on depression and major adverse cardiac and cerebrovascular event (MACCE) occurrence in patients with unprotected left main CAD who underwent CABG.[2] The CRIE program consisted of CAD-related health education, exercise guidance and surveillance, CAD risk factor control, and psychological nursing. Patients in the UC group received discharge guidance. Both groups received a CAD-related health education manual. The CRIE program and UC were administered for 12 months after surgery. Depression was assessed on the day of discharge and at 3, 6, and 12 months. All patients were followed for an additional 24 months after this period or until MACCE occurred. Depression was evaluated by the Hospital Anxiety and Depression Scale—Depression subscale (HADS-D). The HADS-D questionnaire consists of seven items rated on a four-point Likert-type scale, resulting in a maximum score of 21. The severity of depression was graded as follows: 0–7, normal; 8–10, mild; 11–14, moderate; 15–21, severe. The reduction in HADS-D score at 12 months was greater in the CRIE group compared with the UC group (–1.3 vs –0.6, $P<.001$). The percentage of depressed patients at 12 months was lower in the CRIE group

compared with the UC group (15% vs 25%, $P=.043$). Among the depressed patients, no difference was noted in depression severity at 12 months between the CRIE group (65% mild, 30% moderate, 4.3% severe) and UC group (43% mild, 51% moderate, and 5% severe; ANOVA $P=.117$). No difference was noted in MACCE rates between groups ($P=.181$, results presented graphically in article).

A 2018 randomized, double-blind, placebo-controlled trial (n=300) examined the long-term effect of escitalopram on major adverse cardiac events (MACE) in patients with recent acute coronary syndrome.[3] Patients identified as having baseline depression were started on escitalopram 10 mg daily, which could be changed from 5 mg to 20 mg per day during the 24-week treatment period. Patients were followed 5 to 11 years. The primary outcome was the cumulative incidence of MACE. Secondary outcomes included incidence of all-cause mortality, cardiac death, MI, and PCI. Escitalopram reduced composite MACE incidence (hazard ratio [HR] 0.69; 95% CI, 0.49–0.96) and MI (HR 0.54; 95% CI, 0.27–0.96) compared with placebo. No differences were found in the incidence of all-cause mortality (HR 0.82; 95% CI, 0.51–1.33), cardiac death (HR 0.79; 95% CI, 0.41–1.52), or PCI (HR 0.58; 95% CI, 0.33–1.04).

A 2013 double-blinded RCT (n=361) evaluated the effect of six months of escitalopram versus placebo on morbidity and mortality in patients one year post-CABG.[4] The study population consisted of coronary patients at least 30 years old with stable angina pectoris and scheduled to undergo a CABG. Patients took escitalopram 10 mg daily from 14 to 21 days before surgery up to six months after surgery. At 12 months post-CABG, the number of morbidity and mortality events were not different between the escitalopram and placebo groups (60.4% vs 60.3%, $P=.984$). An increase in transient side effects was higher in the escitalopram group compared with placebo (13% vs 4.5%, $P=.006$). A secondary analysis examined the effect of treatment on depression immediately after surgery and at 1-, 3-, 6-, and 12-month intervals. Depression severity was assessed using a 13-item questionnaire, the Beck Depression Inventory Short Form (BDI-SF). Each item is scored from 0 to 3, resulting in a maximum score of 39. The severity of depression was graded as follows: 0–3, normal; 4–7, mild; 8–15, moderate; and 16–39, severe. During the postoperative six-month treatment period, mean decreases in BDI-SF scores were greater overall in the escitalopram group compared with the placebo group ($P=.015$, results presented graphically in article). The mean decrease in BDI-SF scores was most notable in patients with BDI-SF scores greater than 3 at baseline ($P=.002$, results presented graphically in article). EBP

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Do antipsychotics increase the risk of morbidity and mortality in adult hospitalized patients?

EVIDENCE-BASED ANSWER

Maybe. Overall, mortality, delirium severity, hospital and intensive care unit length of stay, and institutionalization are not increased with antipsychotics (SOR: **B**, 2 systematic reviews, 1 meta-analysis of randomized controlled trials and cohort studies). Higher rates of delirium and mortality are associated with typical versus atypical antipsychotics (SOR: **B**, 2 retrospective cohorts). Certain antipsychotics are associated with increased cardiac adverse effects, specifically QTc prolongation (SOR: **C**, disease-oriented evidence).

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

A 2016 systematic review and meta-analysis of 19 studies (N=10,877) including both randomized controlled trials (RCTs) and cohort studies evaluated antipsychotics for preventing and treating delirium.[1] Included were general and intensive care unit (ICU) adult inpatients. Interventions analyzed were use or nonuse of antipsychotics. Studies evaluated duration and severity of delirium, hospital or ICU duration, and institutionalization up to three months after hospitalization. The Delirium Rating Scale (DRS) was used to evaluate severity using an 8- to 16-item scale, with higher scores indicating worse delirium. Antipsychotics did not increase delirium incidence (7 studies, N=1,970), duration (7 studies, N=581), severity (8 studies, N=464), hospital duration (8 studies, N=1,454), ICU duration (7 studies, N=1,400), or 30-day mortality (10 studies, N=1,439). Heterogeneity and varying methodologies limited generalizability.

A 2019 systematic review explored harms and benefits of antipsychotics for delirium in hospitalized adults.[2] Data from 16 RCTs (N=1,768) and 10 observational studies (N=3,839) comparing antipsychotics to each other or placebo were included. Studies without validated instruments were excluded. Nine outcomes were studied: cognitive functioning, hospital duration, delirium severity and duration, sedation, inappropriate continuation of antipsychotics, mortality, cardiac harm, such as myocardial infarction, arrythmias, or QT prolongation and neurologic harm, as defined by extrapyramidal symptoms or neuroleptic malignant syndrome. No difference in mortality was noted in patients given haloperidol compared with placebo or atypical antipsychotics. No increase in hospital stay duration or neurological harm was noted. Although a meta-analysis of three RCTs did not show any increase in QTc with ziprasizone and quetiapine compared with placebo, removal of the single study with quetiapine resulted in a much stronger association (pooled risk ratio 1.95; 95% CI, 1.03–3.71).Limitations were inclusion of critically ill patients and exclusion of patients with preexisting cardiovascular or neurological conditions.

A 2021 retrospective cohort study reviewed the electronic health record of adults in a single U.S. academic institution's ICUs admitted with, or who developed, delirium.[3] Patients already on antipsychotics were excluded. Nearly 8,600 patient encounters assessed mental status, pharmacologic treatment, hospital course, and survival. Daily transition models were constructed to assess mental status, and linear regression models investigated the association of medication administration delirium. The exposure was administration of various antipsychotics. Haloperidol and olanzapine were associated with continued delirium (odds ratio [OR] 1.48; 95% CI, 1.30–1.65; $P<.001$ and OR 1.37; 95% CI, 1.20–1.56; $P=.003$, respectively) and increased in-hospital mortality (hazard ratio [HR] 1.46; 95% CI, 1.10–1.93; $P=.01$ and HR 1.67; 95% CI, 1.14–2.45; $P=.01$, respectively). Quetiapine was associated with decreased in-hospital mortality (HR 0.58; 95% CI, 0.40–0.84; $P=.01$). All antipsychotic use was associated with fewer hospital-free days (95% CI, –1.79 to –0.65; $P<.001$). Use of nonrandomized, uncontrolled, retrospective data and being from a single academic institution were important limitations.

A 2020 retrospective cohort study of 150,948 hospitalizations at a single large academic institution in the United States evaluated whether the risk of death or nonfatal cardiopulmonary arrest was increased in hospitalized adults exposed to antipsychotics.[4] All hospitalizations between 2010 and 2016 were included. Patients admitted to ICU, obstetrics-gynecology, psychiatry, and comfort care were excluded. Patients received typical antipsychotics, usually haloperidol (N=2,681), atypical antipsychotics

(N=10,431), or both (N=1,262). Hospitalizations with exposure to typical antipsychotics were more likely to experience death or cardiopulmonary arrest compared with unexposed hospitalizations (HR=1.6; 95% CI, 1.1–2.4). This persisted when controlling for 39 comorbidities. Exposure to atypical antipsychotics was not associated with death or cardiopulmonary arrest (HR=1.1; 95% CI, 0.8–1.4). Atypical antipsychotics were, however, associated with increased risk of morbidity or mortality in adults 65 years old and older (HR=1.4; 95% CI, 1.1–2.0). Being at a single academic institution and the use of various dosing regimens were limitations of this study. EBP

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