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EVIDENCE-BASED PRACTICE

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EVIDENCE-BASED PRACTICE

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EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

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STATEMENT OF PURPOSE

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

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In patients with behavioral and psychological symptoms of dementia, does deprescribing antipsychotic medication result in worsening symptoms?

CASE

You see an 85-year-old woman with dementia at the nursing home for a routine follow-up visit. She was started on quetiapine six months ago for aggressive behavior toward staff (hitting with personal cares). These behaviors improved after starting quetiapine. Her son has read about the increased risk of mortality with antipsychotic use in people with dementia, and he is wondering whether she should stop taking the quetiapine. He is worried that her behavior might worsen again.

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Bottom Line

Deprescribing antipsychotic medication used for behavioral and psychological symptoms of dementia (BPSD) does not result in worsening symptoms in most patients. There may be some worsening of BPSD with antipsychotic discontinuation in subgroups of patients with more severe baseline BPSD symptoms.

Evidence Summary

Antipsychotics are used to treat dangerous agitation and distressing psychosis in people with dementia, but they are associated with significant adverse events and increased mortality. The 2016 American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia recommended only using antipsychotics when the benefits outweighed the risks and advised attempting to taper and withdraw antipsychotics within four months of initiation unless previous attempts to taper had been unsuccessful.¹

A Cochrane systematic review of 10 RCTs (N=632) assessed the effect of discontinuing antipsychotic medications in patients older than 65 years with dementia.² All patients were on antipsychotic medications at varying doses for at least three months. Most of the trials were conducted in nursing homes although two included patients in community settings. Patients whose

antipsychotic medications were discontinued were compared with patients whose antipsychotic medications were continued. Failure to complete the study was used as a proxy for worsening of BPSD or the need to restart antipsychotic medications. Analyzed individually, seven trials (N=446) found that discontinuation of antipsychotics made little to no difference in whether patients completed the study, while two trials (N=201) including patients with psychosis, agitation or aggression found a higher rate of participants leaving the study early in the antipsychotic discontinuation group (suggesting perhaps a higher rate of BPSD relapse). Seven trials (N=519) found that antipsychotic discontinuation had little to no effect on BPSD symptoms rated on several different scales. Studies that could be pooled showed no difference in BPSD symptoms between groups at three months (2 trials, N=265; mean difference [MD] -1.49; 95% CI, -5.39 to 2.40). However, a subgroup analysis of the same two trials found that in patients with more severe BPSD at baseline, discontinuing antipsychotic medications was associated with worsening BPSD when compared with continuing antipsychotics. Overall, the evidence was rated as low quality, and only one study was assessed as having low risk for bias. Studies were also limited by short follow-up duration (average 19.2 weeks, range 4 weeks to 12 months) and variable types and doses of antipsychotic medications.

Another systematic review and meta-analysis of 10 RCTs (N=663) compared the change in severity of BPSD symptoms in adults with dementia whose antipsychotics were discontinued versus continued.³ The average age of patients was 75 years old or older in all studies, and most lived in long-term care facilities. The duration of follow-up ranged from four weeks to one year. No significant difference was observed in the change in BPSD severity scores in the antipsychotic discontinuation group compared with the continuation group (3 trials, N=214; standardized mean difference [SMD] 0.19; 95% CI, -0.20 to 0.58). However, the antipsychotic discontinuation group had a higher *proportion* of patients with worsening severity of BPSD during the study period (7 trials, N=366; relative risk [RR] 1.78; 95% CI, 1.3–2.4). When

comparing the antipsychotic discontinuation group with the continuation group, there were no statistically significant differences in the rates of early study termination (6 trials, N=462; RR 1.11; 95% CI 0.87–1.41) or the proportion of participants who died during the study (5 trials, N=407; RR 0.83, 95% CI, 0.49–1.39). Only two of the studies were rated as having a low risk of bias, and various antipsychotic medications and doses were used.

A single-arm longitudinal trial (n=133) that was not included in the previous systematic reviews examined the outcomes of an antipsychotic deprescribing intervention in long-term care facilities.⁴ Patients were Australian nursing home residents 60 years old or older taking antipsychotic medications regularly for at least three months. Among patients, 99% had a documented diagnosis of dementia. Residents with a primary psychotic illness such as schizophrenia or bipolar disorder, very severe BPSD, or a terminal illness were excluded. The patients were assessed on two different occasions one month apart before antipsychotic medication discontinuation to assess for baseline changes over time because there was no control group. Nurses, physicians, and pharmacists were educated about nonpharmacological interventions to address BPSD. Study pharmacists created individualized deprescribing protocols for each patient based on best practice guidelines to taper patients off antipsychotic medications. Among patients who remained in the study at three months (N=124), six months (N=110), and 12 months (N=93), the percentage of patients not on regular antipsychotic medications was 86%, 79%, and 82%, respectively. Among the 126 patients who were initially able to stop antipsychotics, regular antipsychotics were restarted for 28 (22%). No significant increase was observed in as-needed antipsychotic prescribing during the intervention; however, the rates of as-needed benzodiazepine use increased from 11% and 8.2% at prebaseline and baseline assessments to 23%, 25%, and 30% at three, six, and 12 months, respectively, albeit at low doses of <10 mg diazepam equivalents per month on average. No statistically significant differences were observed in the secondary outcomes of BPSD symptom scores, falls, hospitalizations, or cognitive scores preintervention and postintervention. This study was limited by potential selection bias because nurses identified patients and may have recruited nursing home patients with less

severe BPSD at baseline. Lack of a control group, loss of patients from the study, and variable types and starting doses of antipsychotic medication were also important limitations. Overall, the study suggested that an interprofessional multicomponent deprescribing intervention in the nursing home setting achieved relatively high rates of deprescribing antipsychotics without worsening BPSD symptoms for many patients.

CASE CONCLUSION

After discussing the risks and benefits of deprescribing antipsychotics, the patient's son agrees with your plan to gradually taper the patient's quetiapine and monitor for worsening BPSD. The nursing staff at the home is appraised of the plan and agrees to review nonpharmacological interventions to address any emergent BPSD.

EBP

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The authors declare no conflicts of interest.

References

1. Reus VI, Fochtmann LJ, Eyler AE, et al. The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. *Am J Psychiatry*. 2016; 173(5):543–546. [STEP 5]
2. Van Leeuwen E, Petrovic M, van Driel ML, et al. Discontinuation of long-term antipsychotic drug use for behavioral and psychological symptoms in older adults aged 65 years and older with dementia. *J Am Med Directors Assoc*. 2018; 19(11):1009–1014. [STEP 1]
3. Pan YJ, Wu CS, Gau SSF, Chan HY, Banerjee S. Antipsychotic discontinuation in patients with dementia: a systematic review and meta-analysis of published randomized controlled studies. *Demen Geriatr Cogn Disord*. 2014; 37(3-4):125–140. [STEP 1]
4. Brodaty H, Aerts L, Harrison F, et al. Antipsychotic deprescription for older adults in long-term care: the HALT study. *J Am Med Directors Assoc*. 2018; 19(7):592–600.e7. [STEP 4]

ACE Inhibitors and ARBs in Advanced CKD—Full Steam Ahead?

Bhandari S, Mehta S, Khwaja A, et al. Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease. *N Engl J Med*. 2022; 387(22):2021-2032. doi:10.1056/NEJMoa2210639

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This multicenter, open-label trial from the United Kingdom evaluated the rate of decline in the estimated glomerular filtration rate (eGFR) at 36 months in adults 18 years old or older with advanced and progressive chronic kidney disease (CKD) who were randomized to continue or discontinue renin-angiotensin system (RAS) inhibition. Patients had progressive stage four or five (eGFR, less than 30 mL per minute per 1.73 m² of body surface area) CKD, were not receiving dialysis, and had not undergone kidney transplant. Patients had to have been on either an angiotensin converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) for at least six months and demonstrated a decrease of at least 2 mL per minute per 1.73 m² per year in eGFR over the previous two years. Multiple exclusion criteria were utilized, most notably myocardial infarction, stroke, or uncontrolled hypertension in the previous three months. A centralized internet-based randomization technique called “minimization” was used to ensure balance in the two groups regarding age, eGFR, diabetes, mean arterial pressure, and proteinuria. The primary outcome showed an eGFR of 12.6 mL per minute per 1.73 m² in the discontinuation group and 13.3 mL per minute per 1.73 m² in the continuation group. The difference of −0.7 (95% CI, −2.5 to 1.0) favors (albeit insignificantly) the outcome in the continuation group. No significant heterogeneity in the primary outcome was observed. Secondary outcomes included a composite measure (≥50% reduction in eGFR, development of ESKD, and starting dialysis) and individual assessments of advancement to end-stage kidney disease (ESKD), starting dialysis, hospitalization, blood pressure, exercise capacity, cardiovascular events and death, as well as hemoglobin and urine protein:creatinine ratio. No secondary outcomes (either disease-oriented or patient-oriented) proved significantly different between groups. During the first year, the discontinuation group had a transient increase in blood pressure as well as the urine protein:creatinine ratio, but little between-group difference was observed thereafter.

Although noteworthy, the generalizability of the trial is concerning. Of the over 17,000 patients from the national database screened, less than 7% (1,210) were considered eligible and only 411 were randomized. In addition, 85% were White, few were very young or very old (median age 63 years old, range 28–91 years), few had diabetic retinopathy (21%), and the withdrawal rate was nontrivial at approximately 20% in each group. As patients had to have been on RAS inhibition without clinically significant side effects before the trial, these patients were possibly less likely to have issues with RAS inhibitors even in advanced CKD. Finally, only 4% of trial patients were on glucagon-like peptide 1 (GLP-1) agonists and only 2% on sodium-glucose cotransporter 2 (SGLT2) inhibitors.

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 Up-to-date, DynaMed, and PubMed with the terms “ACE Inhibitors,” “Angiotensin Receptor Blockers,” and “Chronic Kidney Disease” to find additional literature to place this research into the context of current clinical practice.

Does this meet PURL criteria?

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

Bottom line: This trial provides important data demonstrating no significant difference in the long-term rate of decrease in eGFR in patients with advanced and progressive CKD who remained on or stopped RAS inhibition. Although providing important evidence that has been previously lacking, the generalizability of these results and the overall patient-oriented value of the findings should be considered before being broadly implemented in practice.

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The authors declare no conflict of interest.

Mifepristone for early pregnancy loss: an analysis of clinical cost-effectiveness

Nagendra D, Gutman SM, Koelper NC, et al. Medical management of early pregnancy loss is cost-effective compared with office uterine aspiration [published online ahead of print, 2022 Jun 30]. *Am J Obstet Gynecol.* 2022; S0002-9378(22)00530-0. doi:10.1016/j.ajog.2022.06.054.
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A 2022 study performed a cost and clinical effectiveness analysis for treatment of early pregnancy loss with a combination of mifepristone and misoprostol compared with in-office uterine aspiration. For the medical treatment arm (n=141), data were drawn from a single arm of the previously published 2018 PreFair trial. These women were given a combination of oral mifepristone 200 mg followed by vaginal misoprostol 800 mcg for treatment of early pregnancy loss (defined as an anembryonic pregnancy or fetal demise occurring at less than 12 gestational weeks with a closed cervical os). Researchers from the 2018 study excluded patients with incomplete or inevitable abortion, contraindications to mifepristone or misoprostol, evidence of a viable or ectopic pregnancy, hemoglobin less than 9.5 g/dL, known clotting defect, use of anticoagulants, intrauterine device in place, or unwilling to adhere to study protocol. The comparison arm included data from three previously published studies evaluating in-office uterine aspiration (n not reported). Patients were older than 18 years old (mean age 31) and were reported as demographically similar (although specific aspiration arm demographics were not reported). Length of follow-up was 30 days for determination of need of further medical or surgical treatment based on initial mifepristone/misoprostol pre-treatment success. The primary outcome of treatment effectiveness was determined with a quality-adjusted life years (QALY) model. In general, a QALY model assigns values on a spectrum from one (12-month period of excellent health) to 0 (death). Researchers assumed QALY values for three main study outcomes (adjusted down from a 12-month maximum of 1 to account for the 30-day follow-up period): successful medical treatment (0.083), uterine aspiration (0.0792), and failed medical or surgical treatment (0.075). The primary outcome of cost-

effectiveness was the incremental cost-effectiveness ratio (ICER) which compared the difference in cost treatment with the difference in QALY of each treatment. Analysis of these outcomes revealed that although first-time success rate was higher for uterine aspiration (97% vs 84%, $P=.0001$), medical treatment showed improved QALY compared with aspiration (0.082 vs 0.079; $P<.0001$). Medical management dominant ICER was calculated as $-\$55,883$ per QALY (95% CI, $-\$99,683$ to $\$5,532$). This was interpreted to coincide with a 97.5% chance that medical management was more cost effective than uterine aspiration for all willingness-to-pay thresholds greater than $\$5,600$ per QALY gained. Secondary outcome of cost per person was also lower in the medical treatment group ($\$661$ vs $\$828$; $P=.004$). This study was limited by its secondary analysis of previously published data and lack of specific citation of demographic and outcome data from the uterine aspiration arm. In addition, although standard models for assessing comparative treatment and effectiveness were used, these models required wide-ranging assumptions and estimates of cost (which vary by region) and comparative QALY that are not yet standardized in the field of early pregnancy loss.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching Dynamed and UpToDate with the terms [early pregnancy loss, management] to find additional literature to place this research into the context of current clinical practice.

Does this meet PURL criteria?

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

Bottom line: Medical management of early pregnancy loss with mifepristone and misoprostol likely costs less while maintaining effectiveness when compared with in-office uterine aspiration. Although this study adds helpful analysis about the best treatment options for early pregnancy loss, its suggested intervention (mifepristone

combined with misoprostol, which has previously been shown to be effective) is not immediately implementable for most family medicine physicians because of current FDA regulations on mifepristone use. Because cost-effectiveness is not currently at the forefront of the complicated social, political, and regulatory discourse on mifepristone use, it is unlikely that this analysis alone will lead to a major shift in its use for early pregnancy loss.

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Cholinesterase inhibitors reduce mortality in dementia

Citation: Truong C, Recto C, Lafont C, Canoui-Poitaine F, Belmin JB, Lafuente-Lafuente C. Effect of Cholinesterase Inhibitors on Mortality in Patients With Dementia: A Systematic Review of Randomized and Nonrandomized Trials [published online ahead of print, 2022 Sep 12]. *Neurology*. 2022;10.1212/WNL.0000000000201161. doi:10.1212/WNL.0000000000201161

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A systematic review and meta-analysis was performed on 12 randomized double-blinded placebo-controlled trials (RCT) with 7,272 patients and 12 nonrandomized controlled cohort trials with 71,881 patients. The studies were designed to assess the effect of long-term use of cholinesterase inhibitors (ChIs) on all-cause mortality and cardiovascular mortality in patients with dementia of any type. All studies compared a ChI (donepezil, rivastigmine, galantamine, or tacrine) with placebo or no ChI treatment, followed patients for at least 24 weeks, and reported all-cause mortality or cardiovascular mortality. Although all-cause mortality was the main outcome in the cohort studies, it was not a main outcome in the randomized controlled cohort trials (RCTs). Rather, authors extracted mortality data from the RCTs by examining safety data. Mean ages of patients

ranged from 69 to 85 years old. Study duration was a minimum of six months. ChI was associated with a lower all-cause mortality analyzing crude death rates (19 studies [12 RCTs, 7 cohorts], 29,947 patients, risk ratio [RR] 0.74; 95% CI, 0.66–0.84; $P < .0001$) or analyzing multivariate adjusted hazard ratios (HRs; 11 studies [1 RCT, 10 cohort studies], 63,552 patients, HR 0.77; 95% CI, 0.70–0.84; $P < .00001$). Mortality in the pooled population was 10.7 per 100 person-years in the ChI group compared with 15.1 per 100 person-years in the control group. The estimated number needed to treat (NNT) to avoid 1 death was 29 (95% CI, 22–42). Included RCTs were homogenous in their results ($I^2 = 0\%$), but heterogeneity existed among nonrandomized cohort studies ($I^2 = 80\%–88\%$). Authors attributed heterogeneity to the different settings and populations from which patients were drawn (eg, outpatient clinic, long-term care, general population). Following the GRADE system, the set of RCTs included in the meta-analysis for all-cause mortality were deemed high-quality evidence, whereas the set of cohort studies were low-quality evidence. Only five studies (3 RCTs and 2 cohort studies) provided data on cardiovascular mortality. No heterogeneity was noted between studies ($I^2 = 0\%$). However, the GRADE rating was low-to-moderate quality for this outcome. Treatment with ChIs was associated with a reduction of cardiovascular mortality, analyzing crude death rates (4 studies, 3,112 patients, RR 0.61; 95% CI, 0.40–0.93; $P = .02$) or multivariate-adjusted HR (2 studies, 6,226 patients, HR 0.47; 95% CI, 0.32–0.68; $P < .0001$). In the pooled population, cardiovascular mortality was 3.4 per 100 person-years in patients treated with ChIs and 5.1 per 100 person-years in control patients.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching Uptodate, Dynamed, and Pubmed with the terms dementia and cholinesterase inhibitors to find additional literature to place this research into the context of current clinical practice.

Does this meet PURL criteria?

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

DIVING FOR PURLs

Bottom line: Although the all-cause mortality and cardiovascular mortality in this study are significantly reduced in the CHI patients, several limitations to the information obtained in this study are noted. Heterogeneity in non-RCT studies (which were large and of long duration) was high. In addition, context was not available regarding quality of life, side effects of CHI, and financial/family psychosocial burden associated with long-term care of dementia patients. For these reasons, we cannot recommend this study as a PURL.

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The views expressed in this PURL are those of the author(s) and do not reflect the official policy of the Department of the Army, the Department of Defense, or the U.S. Government.

Does obesity (body mass index ≥ 30 kg/m²) change effectiveness of hormonal contraceptives in women?

EVIDENCE-BASED ANSWER

There is no convincing evidence that obesity alters hormonal contraceptive efficacy (SOR: **B**, systematic review of multiple study designs). The diagnosis of obesity is associated with decreased efficacy of emergency hormonal contraception in some, but not all trials (no SOR given, systematic review of pooled analyses of mostly randomized controlled trials). The American College of Obstetrics and Gynecology recommends that all contraceptive options may be offered to women without regard for the patient's weight (SOR: **C**, consensus societal guideline).

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

A 2016 Cochrane systematic review of 17 studies (randomized controlled trials [RCTs], meta-analyses, and non-comparative studies, N=63,813) examined the effectiveness of hormonal contraceptive methods in women with normal weight and those with the diagnoses of overweight or obesity.¹ Owing to the heterogeneity of the data, a meta-analysis was not possible. The review required that trials and studies reported the contraceptive method, overweight status (measured by weight or body mass index [BMI]), and pregnancy prevention outcome (life table rates, pregnancy rate, or Pearl index which is a calculation of contraceptive efficacy). Trials evaluated combined oral contraceptives (COCs), levonorgestrel (LNG)-ethinyl estradiol or norelgestromin-ethinyl estradiol patches, depot medroxyprogesterone acetate (DMPA), levonorgestrel intrauterine system (LNG-IUS), LNG or etonogestrel implants, and an LNG vaginal ring. There was no significant difference in contraception outcomes in the data for DMPA, LNG-IUS, or the etonogestrel implant. There was discordance across the COC studies, with no clear evidence supporting a change in pregnancy risk with increased BMI. The data from studies that evaluated contraceptive patches and vaginal rings were insufficient to allow any calculation of their potential effect

size between differing weight categories. Limitations of this review included poor to moderate quality trials and lack of recent data for some modalities. The authors also noted that weight is not randomizable and was not the primary comparator of most of the studies. The authors concluded that there was no clear association between hormonal contraceptive method efficacy and weight or BMI.

A 2016 systematic review² evaluated four publications which in total assessed secondary analyses from six RCTs and one single-arm open-label study regarding the efficacy of emergency contraceptive (EC) pills in preventing pregnancy among women diagnosed with obesity (BMI >30 kg/m²) compared with women with BMIs <25 kg/m². All studies used either oral LNG (1.5 mg as a single dose or 0.75 mg repeated at 12 hrs) or oral ulipristal acetate (UPA; either 30 or 50 mg as a single dose) given between 48 and 120 hours after unprotected intercourse. One pooled analysis of two RCTs (N=3,445) measured the likelihood of pregnancy one week after next anticipated menses after using LNG or UPA EC. Women diagnosed with obesity were significantly more likely to become pregnant (OR 3.6; 95% CI 1.96–6.53) than women with a BMI <25 kg/m². When looking at the two EC medications separately, those with BMIs >30 kg/m² using LNG still showed greater likelihood of pregnancy (N=1,731; OR 4.41; 95% CI, 2.05–9.44) while those using UPA only were not (N=1,714; OR 2.62; 95% CI, 0.89–7.0). A second analysis of the same two trials and only assessing women taking LNG (N=1,731) found that pregnancy rates increased from 2% to 6% when weight increased from 70 kg to 80 kg ($P=.0003$). A third pooled analysis from one of the above RCTs and a different single-arm open-label trial compared pregnancy rates among women (N=2,173) taking UPA or LNG EC and found that women with BMIs >30 kg/m² were more likely to become pregnant than women with BMIs ≤ 30 kg/m² (OR 2.1; 95% CI 1.0–4.3). A fourth analysis of three distinct RCTs of women (N=5,863) taking levonorgestrel for EC analyzed pregnancy rates in relationship to both BMI and weight and did not find a significant association between the two. When considering limitations, the four analyses were each graded at poor to fair quality, the original studies were not designed to assess effect of

BMI on emergency contraceptive effectiveness, and weight and height were self-reported in some studies.

A 2019 ACOG Practice Bulletin on hormonal contraception in women with coexisting comorbidities gave recommendations for women with obesity.³ For this “Clinical Management Guideline,” authors performed an evidence review including 19 trials and studies to guide their recommendation. The authors stated that “weight does not significantly affect the effectiveness of hormonal contraceptives” and that “women with obesity may be offered all methods of hormonal contraception” (ACOG level of evidence B: based on limited or inconsistent scientific data). **EBP**

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References

1. Lopez LM, Bernholc A, Chen M, et al. Hormonal contraceptives for contraception in overweight or obese women. *Cochrane Database Syst Rev*. 2016; 2016(8):CD008452. [STEP 2]
2. Jatlou TC, Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. *Contraception*. 2016; 94(6):605–611. [STEP 2]
3. ACOG. *Practice Bulletin: Use of hormonal contraception in women with coexisting medical conditions*. ACOG.org; 2019. <https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2019/02/use-of-hormonal-contraception-in-women-with-coexisting-medical-conditions>. [STEP 5]

Treating gestational diabetes in early pregnancy to decrease adverse neonatal outcomes

Treatment of Gestational Diabetes Mellitus Diagnosed Early in Pregnancy

Simmons D, Immanuel J, Hague WM, et al. Treatment of gestational diabetes mellitus diagnosed early in pregnancy. *N Engl J Med.* 2023; 388(23):2132-2144. doi:10.1056/nejmoa2214956 DOI 10.1097/EBP.0000000000002039

KEY TAKEAWAY: Immediate treatment of gestational diabetes before 20 weeks of gestation leads to a lower incidence of adverse outcomes in neonates compared with no immediate treatment.

STUDY DESIGN: Randomized, single-blinded, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFO: Gestational diabetes is associated with increased risks of complications such as large-for-gestational-age neonates, preeclampsia, shoulder dystocia, etc. Currently, it is unclear whether early treatment of gestational diabetes before 20 weeks of gestation is beneficial in preventing complications of gestational diabetes.

PATIENTS: Women with a singleton pregnancy <20 weeks

INTERVENTION: Immediate treatment of gestational diabetes

CONTROL: No immediate treatment

OUTCOME: Adverse neonatal outcomes, pregnancy-related hypertension, and neonatal lean body mass

SECONDARY OUTCOMES: Various maternal outcomes and neonatal weight and size, neonatal hypoglycemia, and days in NICU

METHODS BRIEF DESCRIPTION:

- Adult women with a singleton pregnancy between four weeks' and 19 weeks and six days' gestation and at least one risk factor for hyperglycemia were included.
- Patients were blinded and randomized to one of the following treatments:
 - Immediate treatment of gestational diabetes with education, dietary advice, instructions on self-monitoring blood glucose level, and insulin therapy if needed
 - Insulin was started if most of the fasting or postprandial glucose values were elevated (fasting glucose greater than or equal to 95 mg/dL or 2-hour postprandial glucose greater than or equal to 120 mg/dL).
 - The treatment group did not get a repeat oral glucose tolerance test at 24 to 28 weeks' gestation.
 - Deferred or no treatment, depending on the results of a repeat oral glucose tolerance test at 24 to 28 weeks' gestation
 - If the repeat oral glucose tolerance test was elevated at 24 to 28 weeks' gestation, patients were treated with treatment measures consistent with the standard of care for gestational diabetes.
- Primary outcomes:
 - The incident of adverse neonatal outcomes including preterm birth before 37 weeks' gestation, birth weight of 4,500 g or greater, trauma during birth, neonatal respiratory distress (distress requiring 4 hours or more of respiratory support with supplemental O₂, CPAP, or intermittent PPV), phototherapy, stillbirth or neonatal death, or shoulder dystocia were collected and combined.
 - Blood pressures were measured during pregnancy for pregnancy-related hypertension (composite of preeclampsia, eclampsia, or gestational hypertension).
 - Neonatal lean body mass was measured with a caliper and calculated with the use of the Catalano equation.
- Secondary outcomes:
 - Maternal: gestational weight gain (weight difference from first to final predelivery visit in kg), cesarean delivery, induction of labor, perineal injury, quality of life (median EQ-5Dsmall-for-gestational-small-for-gestational score at 24–28 weeks)
 - EQ-5D score range 0 to 1, with higher scores indicating better quality of life
 - Neonatal: birth weight, large for gestational age, small for gestational age, mean upper-arm circumference, sum of neonatal caliper measurements, heel-prick blood glucose level (1–2 hours after birth and 72 hours after birth), bed days in NICU, or special care unit

INTERVENTION (# IN THE GROUP): 406

COMPARISON (# IN THE GROUP): 396

FOLLOW UP PERIOD: Until the end of current pregnancy

RESULTS:

Primary Outcome:

- Immediate treatment of gestational diabetes in early pregnancy resulted in a lower incidence of composite adverse neonatal outcomes than no immediate treatment (25% vs 31%; mean difference -5.6%; 95% CI, -10 to -1.2).
- No change in pregnancy-related hypertension (11% vs 9.9%; mean difference 0.7%; 95% CI, -1.6 to 2.9).
- No change in neonatal lean body mass (2.9 vs 2.9 kg; mean difference -0.04; 95% CI, -0.09 to 0.2).

Secondary Outcome:

- No change in maternal gestational weight gain, induction rate, or the percentage of cesarean deliveries.
- Immediate treatment group had lower incidence of severe perineal injury compared with the control group (0.8% and 3.6%; mean difference -2.8; 95% CI, -4.1 to -1.5).
- Immediate treatment group patients had higher quality of life compared with the control group patients (EQ-5D score 0.83 and 0.81; mean difference 0.02; 95% CI, 0.01–0.04).
- No significant differences between the two groups for secondary neonatal outcomes.

Limitations:

- There was no standardized approach to treatment of gestational diabetes.
- Third-trimester treatment targets were used for treatment of early gestational diabetes. These targets had not been tested in early pregnancy.
- Only women with risk factors for hyperglycemia were recruited, rather than broadly screening for early-pregnancy hyperglycemia. EBP

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Vitamin D in prediabetic adults?

Vitamin D and Risk for Type 2 Diabetes in People with Prediabetes

Pittas AG, Kawahara T, Jorde R, et.al. Vitamin D and Risk for Type 2 Diabetes in People with Prediabetes. *Ann Intern Med.* 2023; 176(3):355-363. DOI 10.1097/EBP.0000000000002037

KEY TAKEAWAY: Vitamin D supplementation reduces the risk of developing type 2 diabetes in prediabetic adults.

STUDY DESIGN: Meta-analysis of three RCTs (N=4,190)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFO: Vitamin D is a fat-soluble vitamin that influences glucose metabolism through insulin stimulation in the pancreatic beta cells. Observational studies have shown a correlation between vitamin D deficiency and progression to type 2 diabetes, but the results have been inconsistent. This study assessed whether vitamin D supplementation decreases the risk of new-onset diabetes in prediabetic patients.

PATIENTS: Adults with prediabetes

INTERVENTION: Vitamin D supplementation

CONTROL: Placebo

OUTCOME: New-onset type 2 diabetes

SECONDARY OUTCOME: regression to normal glucose levels, adverse events

METHODS BRIEF DESCRIPTION:

- The three selected trials were from Norway, Japan, and the United States.

- The Norwegian trial used 20,000 IU/week of vitamin D3.
- The US trial used 4,000 IU/day of vitamin D3.
- The Japanese trial used 0.75 mcg/d of eldecalcitol (a hepatically activated vitamin D analog).

PATIENT DEMOGRAPHICS:

- Mean age: 61 years old
- Mean BMI: 30 kg/m²
- Mean vitamin D level was 25 ng/mL
- 44% were women
- 51% were White or European descent, 33% were Asian, and 15% were Black
- 29% of patients were already taking vitamin D supplementation containing less than 4,000IU/d

Primary Outcome

New-onset diabetes was diagnosed using the American Diabetes Association or World Health Organization definitions (HbA1c greater than or equal to 6.5%, fasting blood glucose greater than or equal to 126 mg/dL, or two-hour 75-gram oral glucose tolerance test of greater than or equal to 200 mg/dL).

Secondary Outcomes

Regression to normal glucose levels was defined as having both a normal fasting glucose level (<100 mg/dL) and a normal glucose level two hours after a 75-g oral glucose load (<140 mg/dL). Adverse events included death from any cause, kidney stones, hypercalcemia, and hypercalciuria.

INTERVENTION (# IN THE GROUP): 2,097

COMPARISON (# IN THE GROUP): 2,093

FOLLOW-UP PERIOD: Three years

RESULTS:**Primary outcome**

- Vitamin D reduced the risk for new-onset diabetes compared with the control group (adjusted HR 0.85; 95% CI, 0.75–0.96; NNT=30).

Secondary outcomes

- Vitamin D improved regression to normal glucose levels more than placebo (rate ratio 1.3; 95% CI 1.2–1.5).
- No significant difference was observed in the frequency of adverse events (ie, death, kidney stones, hypercalcemia, and hypercalciuria) between the two groups.

LIMITATIONS:

- The study only evaluated adults with prediabetes. It is unclear whether the same results would be seen in non-diabetic patients or the general population.
- Only three total studies were evaluated.

EBP

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Is cannabis use associated with greater self-harm in patients with mood disorders?

EVIDENCE-BASED ANSWER

Probably. The use of cannabis is associated with a significant increase in self-harm for youth who suffer from mood disorders compared with non-cannabis users (SOR: **B**, large retrospective cohort study and a prospective 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 2021 retrospective cohort study (n=204,780) investigated the association between mortality and self-harm with a new diagnosis of cannabis use disorder.¹ Patients were 10 to 24 years old (65% female; 67% White) with an underlying mood disorder (including bipolar I disorder, dysthymic disorder, cyclothymic disorder, and depressive disorder). Patients were grouped by age and compared with a similar age demographic with an underlying mood disorder, but without cannabis use disorder. Outcomes measured included nonfatal self-harm and all-cause mortality, determined from Ohio Medicaid claims data. The cannabis use disorder group demonstrated greater nonfatal self-harm (adjusted hazard ratio, [aHR] 3.2; 95% CI, 2.6–4.2) and all-cause mortality (aHR 1.6; 95% CI, 1.1–2.2). This included death by unintentional overdose (aHR 2.4; 95% CI, 1.4–4.2) and homicide (aHR 3.2; 95% CI, 1.2–8.6). This study was limited by an assumed underdiagnosis of cannabis use disorder.

A 2021 prospective cohort study (n=6,582) analyzed the relationship between cannabis use and self-harm.² Participants were adolescents 15 to 16 years old (51% female) who screened positive or negative for cannabis use and were followed for self-harm and suicidality over 16 years; 4% of the study population had psychiatric disorder (undefined) at baseline. Self-harm was defined as suicide attempts or deliberate risk-taking outside of recreational activities. The use of cannabis was associated with a significant increase in self-harm compared with non-cannabis use (aHR 2.1; 95% CI, 1.1–6.9). This study was limited by the small number of participants with a listed psychiatric disorder and a lack of statistical analysis comparing patients with and without a psychiatric disorder.

EBP

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References

1. Han B, Compton WM, Einstein EB, Volkow ND. Associations of suicidality trends with cannabis use as a function of sex and depression status. *JAMA Netw Open*. 2021; 4(6):e2113025. [STEP 4]
2. Fontanella CA, Steelesmith DL, Brock G, Bridge JA, Campo JV, Fristad MA. Association of cannabis use with self-harm and mortality risk among youths with mood disorders. *JAMA Pediatr*. 2021; 175(4):377–384. [STEP 3]

What are the most effective strategies to reduce SIDS?

EVIDENCE-BASED ANSWER

The existence of one best method is not clear. Pacifier use is associated with a reduced incidence of sudden infant death syndrome (SIDS) (SOR: **B**, meta-analyses of case-control studies). Multiple other strategies to reduce SIDS include human milk feeding; routine immunization; avoiding exposure to drugs, alcohol, and tobacco; use of a firm, noninclined sleep surface, room sharing without bed sharing, and avoiding soft bedding or overheating (SOR: **C**, expert opinion).

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

A 2005 meta-analysis examined data from seven case-control studies (2,215 cases of sudden infant death syndrome [SIDS] and 6,816 control subjects) from 1966 to 2004 of SIDS among pacifier users compared with a control group.¹ All studies were from Europe or New Zealand. Five studies reported usual and last sleep pacifier use, whereas all seven studies reported last sleep pacifier use. Last sleep was defined as the period of sleep during which the infant died. Using summary odds ratio, authors found a significant reduction risk of SIDS in infants with usual pacifier use at night with multivariate analysis but not with univariate analysis (5 studies; 1,568 cases of SIDS, 5,886 control subjects; univariate odds ratio [OR] 0.90; 95% CI, 0.79–1.03; multivariate OR 0.71; 95% CI, 0.59–0.85). When comparing pacifier used at last sleep, the results were more significant (7 studies; 1,663 cases of SIDS and 5,373 control subjects; univariate OR 0.47; 95% CI, 0.40–0.55; multivariate OR 0.39; 95% CI, 0.31–0.50; number needed to treat=2,733).¹

A 2006 meta-analysis reviewed seven case-control studies and one prospective study when determining if SIDS was reduced with routine pacifier use.² Here, routine pacifier use was more common in the control group compared with SIDS case group (8 studies; 2,042 cases of SIDS; 7,956 control subjects; pooled odds ratio [OR] 0.83; 95% CI, 0.75–0.93). Additionally, authors pooled data from eight case-control studies looking at the relative risk of SIDS associated with pacifier use in the last sleep and found consistent data showing a lower incidence of pacifier use before SIDS (8 studies; 1,984 cases of SIDS; 6,330 control subjects; pooled OR 0.48; 95% CI,

0.43–0.54). The authors of the 2006 meta-analysis noted that these studies did not demonstrate causation and some unmeasurable variable might have been at play.

In their 2022 evidence-based guideline, the American Academy of Pediatrics (AAP) Task Force on Sudden Infant Death Syndrome and the Committee on Fetus and Newborn recommended offering a pacifier at nap time and bedtime to reduce the risk of SIDS (AAP Grade A, based on body of evidence and evaluation of the anticipated balance between benefits and harms when the recommendation is made or based on good-quality patient-oriented evidence).³ Though pacifier use is one recommendation, the AAP offered multiple strategies to reduce SIDS, including human milk feeding; routine immunization; avoiding exposure to drugs, alcohol, and tobacco; use of a firm, noninclined sleep surface, room sharing without bed sharing, and avoiding soft bedding or overheating. **EBP**

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The authors have no conflicts of interest to disclose.

References

1. Hauck FR, Omojokun OO, Siadaty MS. Do pacifiers reduce the risk of sudden infant death syndrome? A meta-analysis. *Pediatrics*. 2005; 116(5):716–723. [STEP 4]
2. Mitchell EA, Blair PS, L'Hoir MP. Should pacifiers be recommended to prevent SIDS? *Pediatrics*. 2006; 117(5): 1755–1758. [STEP 4]
3. Moon RY, Carlin RF; Task Force on Sudden Infant Death Syndrome and the Committee on Fetus and Newborn. Sleep-related infant deaths: updated 2022 recommendations for reducing infant deaths in the sleep environment. *Pediatrics*. 2022; 150(1):e2022057990. [STEP 4]

What is the optimum target blood pressure goal for pregnant persons with chronic hypertension?

EVIDENCE-BASED ANSWER

In pregnant persons with chronic hypertension, treating to a blood pressure less than 140/90 mmHg safely reduces maternal-neonatal adverse outcomes without compromising normal fetal growth (SOR: **B**, large randomized controlled trial). There does not seem to be an increased risk of adverse perinatal outcomes even at treatment pressures less than 120/80 mmHg (SOR: **B**, cohort study). Updated recommendations from two societies now include a treatment threshold of 140/90 mmHg (SOR: **B**, evidence-based guidelines).

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

In 2022, a multicenter, pragmatic, open-labeled, randomized controlled trial (RCT) (n=2,408) addressed the question of whether tight blood pressure (BP) control resulted in lower rates of adverse maternal-perinatal outcomes in pregnant persons with chronic hypertension.¹ Pregnant patients (mean 32 years old), with a known or new diagnosis of chronic hypertension (BP >140/90 mmHg) on or off antihypertensives, with a viable singleton pregnancy before 23 weeks of gestation were randomized to the active treatment group (n=1,208) with goal BP <140/90 mmHg or the control group (n=1,200) in which any existing antihypertensive medication was stopped at randomization and only started if severe hypertension developed (defined as BP ≥160/105 mmHg). Most of the patients were multiparous (84% reported a previous pregnancy), and 67% identified as Hispanic or Black with most common comorbidities being obesity and diabetes mellitus (74% and 16% of the active treatment group, respectively). First-line antihypertensives labetalol or extended release nifedipine were provided to patients per study protocol (62% and 36%, respectively, of the active treatment group), unless the provider or patient stated strong preferences for other antihypertensives (2.4% of the active treatment group). Patients were followed until six to 12 weeks postpartum. The primary outcome was a composite of maternal-perinatal adverse events: preeclampsia with severe features occurring up to two weeks postpartum, medically indicated preterm birth before

35 weeks, placental abruption, or fetal or neonatal death within 28 days of life. Notably, BP >160/100 mmHg alone without proteinuria or other signs of severe features was not classified as preeclampsia with severe features in this trial. The primary safety outcome was delivering a small-for-gestational-age infant (defined as birth weight <10th percentile). The secondary outcome was a composite of maternal cardiovascular complications including death and serious neonatal complications. Compared with the control group, the active treatment group had a significantly lower incidence of composite adverse maternal-perinatal outcomes (30% vs 37%; adjusted RR [aRR] 0.82; 95% CI, 0.74–0.92) without significant increase in newborns with birth weights under 10th percentile for their gestational age (11% vs 10%; aRR 1.04; 95% CI, 0.82–1.3). The NNT to prevent one primary outcome event was 15 (95% CI, 9.4–34). Analysis of secondary maternal and neonatal outcomes indicated that treatment resulted in a lower incidence of severe hypertension (36% vs 44%; RR 0.82; 95% CI, 0.74–0.90), preeclampsia (24% vs 31%; RR 0.79; 95% CI, 0.69–0.89), preterm birth before 37 weeks (28% vs 31%, RR 0.87; 95% CI, 0.77–0.99), and birth weight less than 2,500 gm (19% vs 23%, RR 0.83; 95% CI, 0.71–0.97). The study excluded patients with preexisting cardiac or renal disease, which makes it difficult to extrapolate these findings to the clinical settings where these comorbidities are prevalent.

A 2019 retrospective cohort study of 600 women (mean age 30 years) with singleton pregnancy complicated by chronic hypertension with a mean BP <140/90 mmHg evaluated the safety of lower BP targets in pregnancy.² The majority were multiparous, and more than 70% identified as Black. Patients with pre-existing kidney disease or pregestational diabetes mellitus and other serious comorbidities were excluded from the study. BP was monitored and analyzed as discrete and continuous variables from first to last prenatal visit before delivery or to diagnosis of preeclampsia (whichever came first). The primary outcome was delivery of a small-for-gestational-age (SGA) infant. Secondary outcomes included birth weight, preeclampsia, preeclampsia with severe features, preterm birth occurring before 35 weeks, or composite adverse neonatal outcomes which included perinatal death. Compared with mean SBP of 120 to 139 mmHg and DBP 80 to 89 mmHg, a lower mean BP <120/80 mmHg did not alter the risk for SGA (aOR 1.60; 95% CI, 0.92–2.79). Analysis of secondary outcomes showed a significant decrease in incidence of

preeclampsia with mean BP <120/80 mmHg (SBP aOR 0.45; 95% CI, 0.25–0.90, DBP aOR 0.57; 95% CI, 0.35–0.94). A lower DBP (<80 mmHg) was associated with decreased odds of composite adverse neonatal outcome (aOR 0.45; 95% CI 0.25–0.90), preterm birth before 35 weeks (aOR 0.35; 95% CI 0.2–0.62), and preeclampsia (aOR 0.57; 95% CI 0.35–0.94). A DBP <80 mmHg was associated with an increased birth weight, likely related to the lower risk of prematurity (3,011 gm vs 2,516 gm; $P<.01$). When BP was analyzed as a continuous variable, neither mean SBP <140 mmHg nor mean DBP <90 mmHg was significantly associated with SGA (area under the curve=0.54). Key limitation in this study includes its retrospective design and inability to assess patients' treatment targets or BP goals set by their care team.

In 2022, the American College of Obstetricians and Gynecologists and the Society of Maternal Fetal Medicine issued statements regarding treatment of chronic hypertension in pregnancy.^{3,4} Both organizations recommended treatment threshold of 140/90 mmHg for pregnant patients with chronic hypertension based on the above RCT (no strength of recommendation provided). Both societies' recommendations underwent independent, rigorous review without conflicts of interest or disclosures reported.

EBP

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References

1. Tita AT, Szychowski JM, Boggess K, et al. Treatment for mild chronic hypertension during pregnancy. *N Engl J Med*. 2022; 386(19):1781-1792. [STEP 2]
2. Mitchell CJ, Tita A, Anderson SB, Pasko DN, Harper LM. Adverse outcomes with maternal blood pressure less than 140/90 in pregnancy complicated by hypertension. *Am J Perinatol*. 2019;36(13):1394-1400. [STEP 4]
3. Kaimal AJ, Gandhi M, Pettker CM, Simhan Hyagriv. Clinical guidance for the integration of the findings of the chronic hypertension and pregnancy (CHAP) study. ACOG Practice Advisory; 2022. Accessed February 14, 2023. [STEP 5]
4. Society for Maternal-Fetal Medicine; Publications Committee. Society for Maternal-Fetal Medicine Statement: Antihypertensive therapy for mild chronic hypertension in pregnancy-The Chronic Hypertension and Pregnancy trial. *Am J Obstet Gynecol*. 2022;227(2):B24-B27. [STEP 5]

Is there significant cardiovascular risk associated with long-term phentermine use?

EVIDENCE-BASED ANSWER

In patients without cardiovascular disease, long-term use (>365 days) of phentermine does not cause significant worsening of heart rate or blood pressure. When comparing moderate and long-term use with short-term use, there is no increase in cardiovascular disease or death (SOR: **B**, cohort study). There is no significantly increased risk of composite major adverse cardiovascular events for patients taking phentermine, when used with an average duration of 2.3 months at a time (SOR: **B**, retrospective cohort study).

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

A 2019 cohort study (n=13,972) assessed the cardiovascular safety and effectiveness of long-term phentermine use using electronic health record data.¹ Included patients were 18 to 64 years old (84% female and 45% white) with a body mass index greater than or equal to 27 kg/m² within three months before the first phentermine (<37.5 mg/day) prescription fill. Exclusion occurred in those with a history of bariatric surgery, pregnancy, use of other weight loss medications, diagnosis of cancer, or known cardiovascular disease (CVD). The risk of CVD or death were measured for up to three years after initiating phentermine. Measures of interest included blood pressure (BP), heart rate (HR), and increased risk of incident CVD or death. Follow-up was at six, 12, and 24 months. Short-term use was defined as less than 112

days, reflecting the FDA-approved (at or less than 37.5 mg/day) use of the medication, medium-term use as greater than 112 days but less than 365 days, and long-term use as greater than 365 days. The short-term use group had no significant change in HR at any follow-up interval. The long-term continuous use group had a small increase in heart rate at 24 months (2.6 beats per minute; 95% CI, 0.15–5.1). Systolic BP in the referent group (individuals with 1 phentermine treatment episode lasting ≤ 112 days and no subsequent use during follow-up) was stable at six and 12 months, but at 24 months, it had increased by 1.8 (95% CI, 0.5–3.2) mmHg, relative to baseline. The long-term use group had a decrease in systolic BP of -3.3 mmHg (95% CI, -5.9 to -0.8) at 24 months. Diastolic BP in the long-term group was stable relative to baseline at six, 12, and 24 months. The long-term use group had a -0.69 mmHg (95% CI, -2.5 to 1.2) decrease in diastolic BP compared with the referent group after 24 months. For myocardial infarction, stroke, composite CVD (angina, CABG, or coronary artery intervention), or death, there was no difference when the medium-term and long-term use group was compared with the short-term use group (hazard ratio 1.6; 95% CI, 0.69–3.6). Limitations of this study included uncertain medication adherence and its observational design.

A 2019 retrospective cohort study investigated the extent of major adverse cardiovascular events in patients ($n=616,496$) using phentermine and topiramate (individually or combined) compared with controls.² Patients were mostly female, on average 44 years old, with approximately one-third obese and/or with hypertension and 13% with diabetes. The study found a trend for a lower rate of MACE (major acute CV events) among those with current exposure to phentermine/topiramate than among the unexposed cohort. The average duration of use for phentermine was 2.3 months with the average amount of time for unexposed periods was 7.9 months. Researchers excluded patients with prior weight loss surgery and patients previously using fenfluramine or dex-fenfluramine. The primary outcome was a composite of major cardiovascular events, including hospitalization for acute myocardial infarction or stroke and in-hospital cardiovascular death. The current phentermine use group had fewer major adverse cardiovascular events than the controls (adjusted incidence rate ratio 0.56; 95% CI, 0.34–0.91). There was no difference in the individual incidence rates of acute myocardial infarction, stroke, or cardiovascular related deaths between the phentermine and the control groups. Limitations included variable

duration of medication use and a small number of events creating statistical uncertainty.

EBP

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References

1. Lewis KH, Fischer H, Ard J, et al. Safety and effectiveness of longer-term phentermine use: clinical outcomes from an electronic health record cohort. *Obesity (Silver Spring)*. 2019; 27(4):591–602. [STEP 3]
2. Ritchey ME, Harding A, Hunter S, et al. Cardiovascular safety during and after use of phentermine and Topiramate. *J Clin Endocrinol Metab*. 2018; 104(2):513–522. [STEP 3]

Do antenatal perineal massages decrease the incidence of perineal trauma in labor?

EVIDENCE-BASED ANSWER

Yes. Antenatal perineal massage is associated with a significant decrease in the incidence of third- and fourth-degree perineal tears and episiotomy (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Patients who perform perineal massage from 34 weeks onward are noted to have a significant decrease in perineal trauma requiring suture (SOR: **C**, evidence-based clinical practice guideline).

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

A 2020 meta-analysis of 11 randomized controlled trials (RCTs) (N=3,467) investigated the effect of perineal massage during antenatal care.¹ The mean age of patients was 27.6 years old, and the trials included nulliparous and multiparous women from multiple countries, including Egypt and Canada. The intervention group received antenatal perineal massage within the past four to six weeks before delivery, performed by either the pregnant women or their partner. The control group had no perineal massage. The primary outcome was the risk of first-degree (least severe) to fourth-degree (most severe) perineal tears, and the incidence of episiotomies. Secondary outcomes were duration of second stage of labor, anal incontinence, urinary incontinence, wound healing, and Apgar scores at one and five min. Compared with no perineal massage, antenatal perineal massage was significantly more likely to reduce the risk of all perineal tears (11 trials, N=3,467; relative risk [RR] 0.79; 95% CI, 0.67–0.94; $I^2=65\%$). Specifically, antenatal perineal massage resulted in a significantly lower incidence of third- and fourth-degree perineal tears compared with no perineal massage (7 trials, N=3,069; RR 0.36; 95% CI, 0.14–0.89; $I^2=70\%$), whereas no difference was found in first- and second-degree perineal tears between the two groups. The incidence of episiotomies was also significantly lower in the intervention group than in the control group (11 trials, N=3,467; RR 0.79; 95% CI, 0.72–0.87; $I^2=23\%$). The intervention group had significantly better outcomes than the control group for secondary outcomes as well: decreased duration of the second stage of labor (8 trials, n=1,406; mean difference [MD] –0.06; 95% CI, –0.10 to –0.02; $I^2=34\%$; units not defined), lower risk of anal incontinence (3 trials, N=158; RR 0.30; 95% CI, 0.14–0.66; $I^2=0\%$), and lower risk of suppressed Apgar scores at one min (4 trials, N=549; RR 0.30; 95% CI, 0.06–0.54; $I^2=0\%$) and five mins (4 trials, N=669; RR 0.59; 95% CI, 0.10–1.09; $I^2=86\%$). No significant difference in the incidence of urinary incontinence between the two groups was found. Limitations included that some trials had no blinding.

The American College of Obstetrics and Gynecology (ACOG) released clinical management guidelines on the prevention and management of obstetric lacerations at vaginal delivery in 2018.² In the guideline, a meta-analysis study of four RCTs and quasi-RCTs (N=2,480) was discussed to compare antenatal perineal massage with no massage. Antenatal perineal massage was associated with a decrease in episiotomies among nulliparous women (4 trials, N=2,480; RR 0.84; 95% CI, 0.74–0.95; number needed to benefit [NNTB]=21). Patients who used fingers/hands for perineal massage

from 34 weeks onward reported a significant decrease in perineal trauma requiring suture (4 trials, N=2,480; RR 0.91; 95% CI, 0.86–0.96; NNTB=15). Another meta-analysis of eight RCTs and quasi-RCTs (N=11,651) assessed the effect of perineal techniques during the second stage of labor and the incidence of perineal traumas. Perineal massage during the second stage of labor significantly reduced the incidence of third- and fourth-degree tears when compared with “hands off” the perineum (2 trials, N=2,147; RR 0.52; 95% CI, 0.29–0.94). However, it did not show significant change in the rate of birth with intact perineum. The guideline was given a level B recommendation. There was no specific recommendation for or against antenatal perineal massage. **EBP**

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References

1. Abdelhakim AM, Eldesouky E, Elmagd IA, et al. Antenatal perineal massage benefits in reducing perineal trauma and postpartum morbidities: a systematic review and meta-analysis of randomized controlled trials. *Int Urogynecol J*. 2020;31(9):1735-1745. [STEP 1]
2. Committee on Practice Bulletins-Obstetrics. ACOG practice Bulletin No. 198: prevention and management of obstetric lacerations at vaginal delivery. *Obstet Gynecol*. 2018;132(3):e87-e102. [STEP 5]

Does methylphenidate cause a false positive result on amphetamine drug screening tests in patients on maintenance methylphenidate?

EVIDENCE-BASED ANSWER

Methylphenidate is not detected in methylphenidate-spiked saliva of various concentrations, by commercially available amphetamine and methamphetamine oral fluid drug screening tests (SOR: **C**, in vitro study). Methylphenidate may cross-react as amphetamine in urine drug screening tests, although the effect was documented in urine spiked with high concentrations (200 $\mu\text{m}/\text{mL}$) of methylphenidate (SOR: **C**, in vitro study).

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A 2012 in vitro study assessed the ability of three commercial immunoassays to detect amphetamine-type stimulants (ATSs) (including methylphenidate) in oral fluid.¹ Analytical specificity (cross-reactivity) of amphetamine direct enzyme-linked immunosorbent assay (AMP-ELISA), methamphetamine direct ELISA (MET-ELISA), and Oral-View saliva multidrug of abuse test was evaluated using ATS-spiked oral fluid. The positive cutoff for all three assays was 50 ng/mL. Direct ELISA kits tested fluids at the following concentrations: 50, 100, 150, 250, 500, 1,000, 10,000, 40,000, and 100,000 ng/mL. Oral-View kits tested ATS-spiked fluids at 100 and 500 ng/mL concentrations because of a limited number of kits available. Cross-reactivity was defined as concentration of the target ATS in assay divided by ATS concentration of spiked oral fluid, with the result of this multiplied by 100. This calculation indicated how the assay responded to the target ATS and to other ATSs. Cross-reactivity of methylphenidate was reported as AMP-ELISA: <0.006%, MET-ELISA: <0.002%, and Oral-View <10%, with concentrations falling well below the assay positive cutoff. The authors concluded that none of the kits cross-reacted with methylphenidate, even in high concentrations. A strength of this study was the use of pure reference standard products to evaluate outcomes. Limitations of this study included using in vitro data and lack of urine drug screening evaluation.

A 2002 in vitro study (n=6) evaluated urine samples to determine whether methylphenidate produces

a false-positive urine amphetamine screen.² A 10-mg methylphenidate tablet was used to create 100 $\mu\text{m}/\text{mL}$ and 200 $\mu\text{m}/\text{mL}$ test solutions. The institution's urine drug screen had a positive amphetamine cutoff of 1 $\mu\text{m}/\text{mL}$. Urine samples that tested negative for amphetamines were spiked with the prepared methylphenidate solutions and retested. The resulting samples were assay-positive at the 200 $\mu\text{m}/\text{mL}$ concentration but uniformly negative at 100 $\mu\text{m}/\text{mL}$. These results indicate that methylphenidate may produce a false-positive urine amphetamine screen at higher concentrations. This study was limited by the practice of spiking urine samples with crushed tablets instead of pure reference standards and the use of in vitro data.

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References

1. Souza DZ, Boehl PO, Comiran E, et al. Which amphetamine-type stimulants can be detected by oral fluid immunoassays? *Ther Drug Monit.* 2012;34(1):98-109. [STEP 5]
2. Manzi S, Law T, Shannon MW. Methylphenidate produces a false-positive urine amphetamine screen. *Pediatr Emerg Care.* 2002; 18(5):401. [STEP 5]

Does mode of delivery influence the development of postpartum depression in women of childbearing age?

EVIDENCE-BASED ANSWER

Undergoing cesarean delivery is associated with an increased maternal risk of developing mild postpartum depression 1.3 times the rate seen after spontaneous and instrumental vaginal delivery (SOR: **B**, systematic review and meta-analysis of cohort and cross-sectional studies). Unplanned or emergent cesarean section is associated with a higher risk of post-traumatic stress disorder, which in turn is associated with an increased risk of developing postpartum depression symptoms (SOR: **B**, longitudinal 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 2021 systematic review and network meta-analysis that included 27 cohort and 16 cross-sectional studies (N=1,827,456) and evaluated the risk of postpartum depression (PPD) after delivery.¹ The studies included all postpartum patients of any parity who experienced cesarean section (including elective and emergent) or vaginal delivery (including spontaneous and operative). To evaluate for PPD, the Edinburgh Postpartum Depression Scale (EPDS) was used with a score of 9 to 12 being defined as mild PPD and a score greater than 12 being defined as severe. Analysis of EPDS occurred over three periods: within two weeks postpartum, two to six months postpartum, and greater than six months postpartum. The unadjusted risk of mild PPD occurring after cesarean section was 1.3 times higher than after vaginal delivery (odds ratio [OR]=1.3; 95% CI, 1.2–1.5), with similar results among the three assessment periods (OR=1.4, 1.3, and 1.3, respectively). When adjusting for influential factors related to PPD, the results were consistent with unadjusted results (OR=1.34), indicating that a CS delivery is an important factor of mild PPD. Compared with spontaneous vaginal deliveries, the risk of scoring a high EPDS score was 1.53 times more likely after emergent cesarean section (28 trials, n=unknown; OR 1.5; 95% CI, 1.2–1.9) and 1.47 times more likely after elective cesarean section (27 trials, n=unknown; OR 1.5; 95% CI, 1.2–1.9). There was no significant difference in the risk of severe PPD in cesarean section compared with vaginal delivery (OR=1.1; 95% CI, 0.99–1.7).

A 2022 secondary analysis of data from the Alberta Pregnancy Outcomes and Nutrition (APrON) longitudinal cohort study (N=354) was performed to investigate the association between cesarean section type (planned vs unplanned/emergency) and PPD and whether postpartum post-traumatic stress disorder (PTSD) symptoms mediated this association.² This study included pregnant women older than 16 years of age and less than 27 weeks' gestation at time of enrollment living in either Edmonton or Calgary, Canada, with singleton deliveries through cesarean section. PPD symptoms were measured at three months postpartum and evaluated by EPDS screening, and PTSD symptoms were measured using the Psychiatric Diagnostic Screening Questionnaire (PDSQ). PPD development was not directly associated with either type of cesarean section (correlation coefficient [β]=0.45; 95% CI, -0.39 to 1.3). However, PTSD was positively associated with having a cesarean section of either type (β =0.44; 95% CI, 0.07–0.8), and there was a positive association between PPD and PTSD (β =0.56; 95% CI, 0.32–0.81). Specifically, mothers who experienced an emergency or unplanned cesarean section had increased PTSD scores by nearly 0.44 of a point compared with those who had a planned cesarean section. PPD symptoms were indirectly associated with cesarean section in those patients with PTSD symptoms (β =0.025; 95% CI, 0.04–0.52). The sample underrepresents women in lower education and income categories, thereby impacting the generalizability of the results.

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References

1. Sun L, Wang S, Li XQ. Association between mode of delivery and postpartum depression: a systematic review and network meta-analysis. *Aust N Z J Psychiatry*. 2021; 55(6): 588–601. [STEP 2]
2. Grisbrook MA, Dewey D, Cuthbert C, et al. Associations among caesarean section birth, post-traumatic stress, and postpartum depression symptoms. *Int J Environ Res Public Health*. 2022; 19(8):4900. [STEP 3]

Does statin use reduce the risk of dementia?

EVIDENCE-BASED ANSWER

Statin use in patients at high risk for vascular events late in life does not decrease the incidence of dementia or alter cognitive status in up to five years of follow-up (SOR: **A**, systematic review of randomized controlled trials).

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A 2016 systematic review and meta-analysis of two randomized controlled trials (RCTs; N=26,340) examined the effectiveness of statins on the prevention of dementia in adults at high risk for vascular events, defined as males at least 65 years old with hypertension, or anyone having a medical history of diabetes, coronary heart disease, stroke, transient ischemic attack, or other occlusive arterial disease.¹ Patients were between 40 and 82 years old (44% were 70 years or older) who lived in the United Kingdom, Ireland, or the Netherlands. Patients assigned to the treatment group received simvastatin 40 mg or pravastatin 40 mg daily, whereas the control group patients received matching placebos. The primary outcomes of the review included the incidence of dementia (diagnostic criteria not reported), cognition (at study end or as change from baseline), and adverse events, reported at a mean of five (n=20,536) and 3.2 (n=5,804) years of follow-up. One study (n=20,536) measured cognitive impairment at the study end using the modified Telephone Interview for Cognitive Status. The other trial (n=5,804) evaluated the change in cognition from baseline with a combination of the Mini Mental Status Examination (MMSE; scale 0–30, lower numbers indicated worsening global cognitive function), number of correct letter digit codes within 60 seconds (lower numbers indicated worsening processing speed), number of words remembered in the Picture-Word Learning Test (scale 0–15; lower numbers indicated worsening immediate and delayed recall), and time needed to complete the Stroop Test (longer time indicated worsening attention).

Statins compared with placebo did not decrease the incidence of dementia (1 trial, n=20,536; 31 vs 31 cases; odds ratio [OR] 1.0; 95% CI, 0.61–1.7) nor did they alter the risk of cognitive impairment (1 trial, n=20,536; OR 0.97; 95% CI, 0.91–1.0) at five-year follow-up. Statins also did not significantly affect change in cognition from baseline to 3.2 years based on any of the measures of cognition including the MMSE (1 trial, n=5,804; mean difference [MD] 0.06; 95% CI, –0.04 to 0.16), number of correct letter digit codes (1 trial, n=5,804; MD –0.01; 95% CI, –0.25 to 0.23), number of words remembered in the Picture-Word Learning Test (1 trial, n=5,804; MD 0.02; 95% CI, –0.12 to 0.16), or time needed to complete the Stroop Test (1 trial, n=5,804; MD 0.8 seconds; 95% CI, –0.38 to 2.0 seconds). No significant differences were noted in rhabdomyolysis (2 trials, N=26,340; 5 vs 3 cases; OR 1.7; 95% CI, 0.40–7.0) or myalgias (1 trial; n=5,804; 36 vs 32 cases; OR 1.1; 95% CI, 0.70–1.8) in the statin groups compared with the placebo groups. Both RCTs had low risk of bias, although the evidence was limited by the fact that cognition was a tertiary endpoint in both RCTs.

In contrast, a 2018 systematic review and meta-analysis identified 25 prospective cohort studies (N=4,580,015) evaluating the effect of statin therapy for hyperlipidemia on the risk of developing dementia or Alzheimer disease (AD).² The review did not provide detailed information about the patients; however, the majority (>70%) were more than 50 years old. Patients received both high-potency (eg, atorvastatin, rosuvastatin, and simvastatin) and low-potency (eg, fluvastatin, lovastatin, and pravastatin) statin therapy. No information was noted regarding interventions for the comparison groups in these studies. The pertinent outcome was all-cause dementia or AD; however, methods for diagnosis were not defined. Duration of follow-up ranged from 2.4 to 24.9 years. Statin use was associated with a reduced risk of dementia (17 studies, N=4,133,183; RR 0.77; 95% CI, 0.63–0.95) and AD (13 studies, N=1,192,510; RR 0.86; 95% CI, 0.80–0.92) compared with the control group patients. Subgroup analyses by study quality, follow-up time, or number of cases did not significantly affect these associations. However, because these were all cohort studies, the results do not invalidate the earlier meta-analysis of RCTs.

EBP

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References

1. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. *Cochrane Database Syst Rev*. 2016; 2016(1):CD003160. [STEP 1]
2. Larsson SC, Markus HS. Does treating vascular risk factors prevent dementia and alzheimer's disease? A systematic review and meta-analysis. *J Alzheimers Dis*. 2018; 64(2):657–668. [STEP 1]

Does vitamin E help with improving non-alcoholic fatty liver disease?

EVIDENCE-BASED ANSWER

There is no evidence it improves patient-oriented outcomes. Adding vitamin E supplementation to adult patients with nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis without comorbid conditions results in small improvements in steatosis, lobular inflammation, and hepatocellular ballooning (SOR: **C**, meta-analysis of randomized controlled trials [RCTs] with disease-oriented evidence). In adult and pediatric patients with a diagnosis of NAFLD without evidence of comorbid conditions, supplementation with vitamin E yields no clinically significant difference in body mass index, liver enzyme levels, or histological findings (SOR: **C**, meta-analysis of RCTs with disease-oriented evidence).

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A 2020 meta-analysis of seven randomized controlled trials (RCTs) (N=465) evaluated the effect of vitamin E supplementation or placebo on biochemical and histological parameters in adults with nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH).¹ The duration of the RCTs ranged from 8 to 96 weeks. Patients

received either 400- to 800-mg vitamin E daily or matched placebo. Trials were conducted on adults from Iran, Malaysia, Pakistan, and the United States. Inclusion criteria were adult patients diagnosed with NAFLD or NASH according to international definitions. Patients with heavy alcohol consumption or inflammatory liver diseases were excluded. Overall, patients given vitamin E had a statistically significant decrease in alanine aminotransferase [ALT] (8 trials, N=465; mean difference [MD] -7.4 IU/L; 95% CI, -10 to -4.6) and aspartate transaminase [AST] (8 trials, N=465; MD -5.7 IU/L; 95% CI, -9.5 to -1.9). They also showed significant improvement in histological characteristics of NASH including steatosis (8 trials, N=465; MD -0.61; 95% CI, -0.89 to -0.34), lobular inflammation (8 trials, N=465; MD -0.31; 95% CI, -0.52 to -0.1), hepatocellular ballooning (8 trials, N=465; MD -0.32, 95% CI -0.53 to -0.1), and liver fibrosis (8 trials, N=465; MD -0.26; 95% CI, -0.47 to -0.04). Limitations of this meta-analysis included a low number of patients in these trials and sampling variability in one trial.

A 2019 meta-analysis of nine RCTs (N=889) evaluated the effect of vitamin E therapy on improving outcomes in patients with NAFLD.² One RCT overlapped with the previous meta-analysis. The analysis included both adults and children with the mean ages ranging from 9.9 to 59 years, with 31% to 75% male. Inclusion criteria were patients with a diagnosis of NAFLD, which was defined as lipid deposition in the liver without significant history of alcohol consumption or other secondary causes. Duration of the RCTs ranged from six months to four years. Patients were given vitamin E at various doses (80–1,000 IU daily) compared against a placebo. Measured outcomes included body mass index (BMI) and ALT/AST changes. Adjuvant vitamin E therapy was associated with no difference in AST, ALT, or BMI in either adults or children. No statistically significant change in hepatocellular ballooning score or fibrosis score was noted. Limitations included less data for the pediatric population compared with the adult population and wide variations in demographics, dosing of vitamin E, and follow-up duration in the included trials.

EBP

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References

1. Vadarlis A, Antza C, Bakaloudi DR, et al. The effect of vitamin E supplementation in liver enzymes, histology and metabolic biomarkers in adult patients with non-alcoholic fatty liver disease (NAFLD). A systematic review and meta-analysis. *Clin Nutr ESPEN*. 2020; 40:458–459. [STEP 1]
2. Amanullah I, Khan YH, Anwar I, Gulzar A, Mallhi TH, Raja AA. Effect of vitamin E in non-alcoholic fatty liver disease: a systematic review and meta-analysis of Randomised Controlled Trials. *Postgrad Med J*. 2019; 95(1129):601–611. [STEP 1]

In adult women with stress urinary incontinence, do pelvic floor muscle exercises improve incontinence severity and therefore quality of life?

EVIDENCE-BASED ANSWER

Yes. In women with stress urinary incontinence (SUI), pelvic floor muscle exercises are associated with a greater cure rate at three to six months with a number needed to treat of two when compared with placebo or no therapy (SOR: **A**, systematic review of randomized controlled trials [RCTs]), and perhaps a 13% to 25% improvement in several quality of life measures (SOR: **C**, small RCT). The American College of Physicians recommends pelvic floor muscle training as first-line treatment for women with SUI (SOR: **C**, clinical guideline).

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A 2018 systematic review and meta-analysis of 17 randomized controlled trials (RCTs) and one quasi-randomized trial (N=1,355) from 11 countries evaluated the effectiveness of pelvic floor muscle therapy (PFMT) for women with SUI.¹ Patients were nonpregnant women

with a mean age range of 45 to 77 years old without cancer, underlying neurological disorders, or significant cognitive impairment. Patients assigned to PFMT engaged in various programs of repeated voluntary pelvic floor muscle contractions, typically taught and supervised by healthcare professionals over four weeks to six months. Those assigned to the comparison arm received no treatment, placebo drugs, sham treatments, or other inactive control (eg, advice on incontinence pads or lifestyle interventions). The primary outcomes were patient-perceived symptomatic cure of SUI, symptoms of cure or improvement, and symptom-specific and condition-specific QOL measures. Secondary outcomes included the number of leakage episodes in 24 h. Women in the PFMT groups were more likely to report symptomatic cure (4 trials, N=165; 56% vs 6%; relative risk [RR] 8.4; 95% CI, 3.7–19.1; number needed to treat [NNT]=2) and symptoms of cure or improvement (3 trials, N=242; 74% vs 11%; RR 6.3; 95% CI, 3.9–10.3; NNT=2) at three to six months compared with women in the control group. Women in the PFMT versus control group were also more likely to report significant improvement in most QOL measures (TABLE). PFMT was associated with about one fewer leakage episode per 24 h compared with the control intervention (7 trials, N=432; mean difference [MD] –1.2; 95% CI, –1.8 to –0.68). One major limitation of this review was the absence of a clear description of the PFMT programs and their variability across trials. Trials were limited by the absence of long-term follow-up with most treatments being relatively short (ie, 4 weeks to 6 months). In addition, four of the 18 trials were considered at high risk of bias.

A 2020 multicenter RCT (n=74) examined the effectiveness of PFMT for SUI.² The trial included women ages 60 to 78 years old (mean age 70 years old) diagnosed by a urology specialist with SUI and excluded patients with any contraindication to PFMT, a diagnosis of mixed or urge UI, or recent UI treatments. The study randomly assigned patients to receive 12 sessions of PFMT supervised by a physiotherapist (experimental group; n=40) or no therapy (control group; n=34). The primary outcome was the difference in self-reported assessments of symptoms and QOL (based on the King's Health Questionnaire) measured at the beginning and at the end of a four-week treatment duration. Patients in the PFMT group had a 12.5% decrease in SUI symptoms ($P<.001$) compared with a 6.2% increase in the control group ($P=.19$). Patients in the PMFT groups had significant percentage improvements

TABLE. QOL outcomes from meta-analyses of RCTs comparing PFMT with control interventions (ie, no treatment, placebo drugs, sham treatments, or other inactive control) in women with stress urinary incontinence¹

Outcome measure (score range); lower scores=improved QOL	No. of RCTs	No. of patients	Mean difference PMFT vs control ^a (95% CI)
ICIQ-LUTSqol (19–76)	1	118	–5.3 (–7.7 to –2.9)
ICIQ-UI short form (0–21)	3	196	–3.5 (–4.4 to –2.5)
IIQ (0–100)	1	35	–19.7 (–30.6 to –8.8)
I-QOL (0–100)	1	50	–24.6 (–37.8 to –11.5)
KHQ severity (0–100)	3	145	–13.2 (–2.1 to –5.2)
KHQ impact (0–100)	3	145	–13.4 (–32.2 to 5.4)
KHQ physical limitation (0–100)	3	145	–11.9 (–20.6 to –3.2)
KHQ general health (0–100)	3	145	–1.8 (–3.4 to 7.0)
UDI short form (0–100)	1	35	–16 (–29.8 to –2.2)

Results in bold font are statistically significant. ^a For mean differences, negative numbers favor PMFT over control interventions. ICIQ-LUTSqol=International Consultation on Incontinence Modular Questionnaire—Lower Urinary Tract Symptoms Quality of Life; ICIQ-UI=Incontinence Modular Questionnaire—Urinary Incontinence; IIQ=Incontinence Impact Questionnaire; I-QOL=Incontinence-specific Quality of Life questionnaire; KHQ=King's Health Questionnaire; UDI=Urinary Distress Inventory.

in QOL measures over four weeks as follows: severity (25%; $P<.001$), social limitations (22%; $P=.001$), emotions (17%; $P=.04$), and bladder-related symptoms (13%; $P<.001$). PMFT did not significantly improve QOL in terms of role or physical limitations, personal relationships, and sleep or energy; patients in the control groups reported no statistically significant changes in any of the QOL measurements. This RCT was limited by the lack of blinding of the patient and physiotherapist to the group assignments.

In 2014 the American College of Physicians evidence-based clinical practice guideline for the nonsurgical management of urinary incontinence recommended pelvic floor muscle training as first-line treatment for women with SUI (strong recommendation based on high-quality evidence).³ The guideline was based on a systematic review sponsored by the Agency for Healthcare Research and Quality. **EBP**

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References

1. Dumoulin C, Cacciari LP, Hay-Smith EJC. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. *Cochrane Database Syst Rev*. 2018; 10:CD005654. [STEP 1]
2. Wber-Rajek M, Straczynska A, Strojek K, et al. Assessment of the effectiveness of plevic floor muscle training (PFMT) and extracorporeal magnetic innervation (ExMI) in treatment of stress urinary incontinence in women: a randomized control trial. *Biomed Res Int*. 2020; 2020:1019872. [STEP 2]
3. Qaseem A, Dallas P, Forciea MA, et al. Nonsurgical management of urinary incontinence in women: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2014; 161:429–440. [STEP 5]

In overweight adult patients with type 2 diabetes, is tirzepatide as effective for weight loss compared to existing GLP1 agonists (i.e. Ozempic)?

EVIDENCE-BASED ANSWER

Perhaps. Tirzepatide (5, 10, or 15 mg weekly) is superior to low-dose semaglutide (1 mg weekly) for weight loss in patients with type 2 diabetes (SOR **B** randomized controlled trial [RCT]). High dosages of tirzepatide (10 or 15 mg weekly) result in greater weight loss than low-dose dulaglutide (1.5 mg weekly) in patients with type 2 diabetes (SOR **B**: RCT).

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A 2021 open-label, randomized-controlled phase 3 clinical trial (n=1,878) compared the efficacy and safety of tirzepatide and semaglutide in patients with type 2 diabetes uncontrolled with metformin alone.¹ Patients were 18 years old or older, treated with at least 1,500 mg daily of metformin, with a HbA1c of 7.0 to 10.5%, a body mass index (BMI) of at least 25 kg/m², and a stable weight ($\pm 5\%$) during the previous three months. Patients were 53% female, mean age was 57 years old, mean bodyweight was 94 kg, and mean HbA1c was 8.3%. Researchers excluded patients with type 1 diabetes, an estimated glomerular filtration rate below 45 mL/minute, a history of pancreatitis, and a history of diabetic retinopathy or maculopathy. Patients received either once-weekly subcutaneous tirzepatide at doses of 5 mg, 10 mg, or 15 mg (n=470/469/470) or subcutaneous semaglutide 1 mg (n=469) for 40 weeks. Tirzepatide was started at 2.5 mg once weekly and titrated upward by 2.5 mg every four weeks until the assigned dose was reached. Semaglutide was started at 0.25 mg once weekly and titrated upward by doubling the dose every four weeks until 1 mg was reached. Patients were followed for an additional four weeks to evaluate safety. The primary outcome was the change in HbA1c from baseline to week 40. A key secondary outcome was change in bodyweight from baseline to week 40. Tirzepatide 5 mg, 10 mg, and 15 mg and semaglutide 1 mg resulted in bodyweight reductions of -7.6 kg, -9.3 kg, -11.2, and -5.7 kg, respectively. Tirzepatide at all dosages resulted in greater weight loss than 1 mg semaglutide (for 5 mg tirzepatide, mean difference [MD] -1.9 kg,

95% CI, -2.8 to -1.0; for 10 mg MD -3.6 kg, 95% CI, -4.5 to -2.7; and for 15 mg MD -5.5 kg, 95% CI, -6.4 to -4.6). Weight loss was sustained and did not plateau in the four treatment groups. Adverse events occurred in 64 to 69% of patients taking tirzepatide and semaglutide, with the most common being mild-to-moderate gastrointestinal effects (nausea, diarrhea, and vomiting). Patients taking tirzepatide had more serious adverse events compared with patients taking semaglutide (5.3–7% vs 2.8%; *P* value not provided). A notable limitation of this study was that the higher doses of semaglutide, which are approved for weight loss (2–2.4 mg weekly), were not included in the comparison groups. Tirzepatide is not Food and Drug Administration (FDA)-approved for weight loss. Other limitations include the open-label study design, the duration of 40 weeks (only allowing for 16 weeks at the highest tirzepatide dose), and the low representation of African American patients. The study was funded by the manufacturer.

A 2018 double-blind, randomized-controlled phase 2 clinical trial (n=318) compared tirzepatide with dulaglutide and placebo in patients with type 2 diabetes.² Patients were 18 to 75 years old with an HbA1c between 7.0 to 10.5% for at least six months, inadequately controlled with diet and exercise alone or metformin, and a BMI of 23 to 50 kg/m². Patients were 47% female, mean age was 57 years old, and mean BMI was 33 kg/m². Patients received either once-weekly subcutaneous tirzepatide at doses of 1 mg, 5 mg, 10 mg, or 15 mg (n=53/55/52/53); subcutaneous dulaglutide 1.5 mg (n=54); or placebo (n=51) for 26 weeks. Patients assigned to tirzepatide 1 mg or 5 mg or dulaglutide 1.5 mg were started at these doses without dose titration. Patients assigned to tirzepatide 10 mg or 15 mg were started at 5 mg for the first two weeks and then increased to 10 mg. The dose was increased to 15 mg after four weeks for patients assigned to this dose. The primary outcome was change in HbA1c from baseline to 26 weeks. Secondary endpoints of interest included change in mean bodyweight and proportion of patients with at least 5% and 10% bodyweight loss. A greater weight reduction was observed in patients taking tirzepatide 10 mg or 15 mg compared with patients taking dulaglutide (-8.7 kg with 10 mg, -11.3 kg with 15 mg vs -2.7 kg with dulaglutide; *P*<.05 for each comparison). However, tirzepatide 1 mg and 5 mg did not significantly reduce mean bodyweight compared with dulaglutide (-0.9 kg and -4.8 kg vs -2.7 kg with dulaglutide; *P*>.05). Bodyweight

reductions were dose-dependent with tirzepatide. A greater proportion of patients taking tirzepatide 5 mg, 10 mg, and 15 mg lost 5% and 10% of their bodyweight compared with patients taking dulaglutide (47%, 71%, 62% vs 22%; $P<.05$ for each comparison and 16%, 39%, 38% vs 9.3%; $P<.05$ for tirzepatide 10 mg and 15 mg). The most common adverse events for tirzepatide were gastrointestinal (nausea, diarrhea, and vomiting), with the incidence being dose-related (from 23% to 66% with tirzepatide and 43% for dulaglutide). Limitations of this study included the small sample size, the short duration of 26 weeks, and the lack of comparison with higher doses of dulaglutide (3 mg and 4.5 mg). Dulaglutide is not FDA-approved for weight loss. This study was funded by the manufacturer. **EBP**

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References

1. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med*. 2021;385(6):503-515. [STEP 2]
2. Frías JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet*. 2018;392(10160):2180-2193. [STEP 2]

In patients with type 2 diabetes, do glucagon-like peptide-1 receptor agonists reverse non-alcoholic fatty liver disease?

EVIDENCE-BASED ANSWER

In patients with diabetes mellitus type 2 and non-alcoholic fatty liver disease, the use of glucagon-like peptide-1 receptor agonists leads to a 3% greater reduction in intrahepatic adipose content over other standard treatments for type 2 diabetes. Hepatic enzymes, total body weight, and body mass index also decrease (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Treatment with liraglutide results in a greater reduction in intrahepatic fat concentration than treatment with gliclazide. (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 2021 systematic review included eight randomized controlled trials (RCTs) (N=468) and evaluated the effectiveness of glucagon-like peptide-1 receptor agonists (GLP-1 RA) in decreasing hepatic steatosis for patients with diabetes mellitus type 2 (DM-2).¹ Adult men and women with a diagnosis of diabetes and nonalcoholic fatty liver disease (NAFLD) were included in the study. Patients with secondary causes of hepatic disease were excluded. Patients were followed for 12 weeks (2 trials, N=86), 24 weeks (4 trials, N=228), or 26 weeks (2 trials, N=166). Patients received either liraglutide 1.8 mg daily (4 trials, N=252), liraglutide 1.2 mg daily (1 trial, N=60), exenatide 20 µg daily (1 trial, N=71), exenatide 10 µg twice daily (1 trial, N=33), or dulaglutide 1.5 mg weekly (1 trial, N=64). Those patients receiving a GLP-1 RA were compared with those who had received insulin (5 trials, N=237), pioglitazone (2 trials, N=82), sitagliptin (2 trials, N=85), or a placebo (2 trials, N=95). Magnetic resonance spectroscopy was used to evaluate for the primary outcome—change in intrahepatic adipose (IHA) content. Secondary outcomes included changes in hepatic enzyme levels, total body weight, and body mass index (BMI). When compared with current treatment options for diabetes, the use of GLP-1 RAs decreased IHA content by an average of three additional percentage points (weighted mean difference [WMD] −3.0; 95% CI, −4.8 to −1.3). The administration of GLP-1 RAs also resulted in a reduction of ALT values (WMD −3.8 U/L; 95% CI, −7.0 to −0.6), AST values (WMD −2.4 U/L; 95% CI, −4.6 to −0.3),

total body weight (WMD -3.5 kg; 95% CI, -4.6 to -2.4), and BMI (WMD -1.1 kg/m²; 95% CI, -1.4 to -0.8). Reported side effects from the use of GLP-1 RAs included nausea, vomiting, diarrhea, and asymptomatic hypoglycemia.

A 2017 single-center RCT ($n=87$, not included in the data analysis of the above systematic review) evaluated liraglutide's efficacy in reversing hepatic steatosis in patients with NAFLD.² Patients included 18 to 70-year-old men and women with a BMI between 20 and 38 kg/m², a glycosylated hemoglobin between 7% and 14%, and an intrahepatic fat (IHF) content greater than or equal to 10%. Excluded patients had AST values greater than or equal to 2.5-fold the upper limit of normal, a GFR less than 60 mL/min, a history of autoimmune or viral liver disease, congestive heart failure, or excessive alcohol consumption (>2 drinks per day for women, >3 drinks per day for men). Patients were followed for 24 weeks and randomized into one of three open-label groups. Patients in the liraglutide group ($N=31$) were started on 0.6 mg/day for the first week, 1.2 mg/day during the second week, and 1.8 mg/day for the remaining 22 weeks. Patients in the metformin group ($N=31$) were started on 250 mg three times a day for the first week, 500 mg three times a day for the second week, and 1,000 mg twice a day for the remaining weeks. Patients in the gliclazide group ($N=31$) received an initial dosage of 30 mg and were titrated up to a maximum of 120 mg daily. At the beginning and at the end of the study, all patients underwent ultrasonography to measure IHF content. Overall decrease in IHF content served as the primary outcome. Secondary outcomes included changes in total body weight, changes in liver enzyme values, and changes in triglyceride levels. Relative to the baseline IHF measurement, a significant decrease in IHF content was noted within all three study groups after 24 weeks—the liraglutide group saw a decrease from 37% to 13% ($P<.001$); the metformin group saw a decrease from 35% to 18% ($P<.001$); the gliclazide group saw a decrease from 33% to 20% ($P<.001$). The absolute IHF reduction seen in the liraglutide group (24 percentage points) was greater than the reduction seen within the gliclazide group (13 percentage points; $P=.001$). A comparison between IHF loss with liraglutide and metformin was provided graphically without statistical analysis. Weight loss within the liraglutide group also reached statistical significance (mean weight change -5.6 kg, $P<.001$). Decreases in ALT (mean change -22 U/L, $P<.01$), AST (mean change -7.2 U/L, $P<.01$), and triglyceride levels (mean change -0.9 mmol/L, $P<.01$) were also noted within the liraglutide

group. Appetite suppression (76%), diarrhea (14%), nausea (10%), and abdominal distension (10%) were reported as side effects in the liraglutide group, but none of these symptoms resulted in patients discontinuing the medication. **EBP**

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References

1. Zhu Y, Xu J, Zhang D, et al. Efficacy and safety of GLP-1 receptor agonists in patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2021; 12:769069. [STEP 1]
2. Feng W, Gao C, Bi Y, et al. Randomized trial comparing the effects of gliclazide, liraglutide, and metformin on diabetes with non-alcoholic fatty liver disease. *J Diabetes*. 2017; 9(8): 800–809. [STEP 2]

Is naltrexone/bupropion an effective adjunct therapy to lifestyle modification in weight loss?

EVIDENCE-BASED ANSWER

Adding naltrexone/bupropion to lifestyle modification improves weight loss compared with lifestyle modification alone (SOR: **A**, based on 3 randomized controlled trials and meta-analysis).

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

In 2016, a meta-analysis including 28 randomized controlled trials (RCTs) (N=29,018) compared the efficacy of five weight loss medications.¹ The review included patients with a BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² or who had one or more weight-associated comorbidities. Patients were treated with orlistat, lorcaserin, naltrexone–bupropion, phentermine–topiramate, or liraglutide for at least one year. The primary outcome was the number of patients achieving at least 5% weight loss after one year, with secondary outcomes being weight loss of 10% and risk of discontinuation of therapy because of adverse events. All the approved agents were associated with at least 5% weight loss at 52 weeks, with naltrexone/bupropion having an average of 5.0 kg weight loss at one year (95% CI, –5.94 to –3.96). Naltrexone/bupropion was also associated with the highest discontinuation rate because of adverse effects (OR, 2.64; 95% credible interval [CrI,] 2.10–3.35). The meta-analysis was limited by heterogeneity in study design and differences in cointerventions among studies compared.

A multicenter RCT (n=1,496) studied combined naltrexone sustained release (SR) (32 mg/day) plus bupropion SR (360 mg/day) (NB32) versus placebo for weight loss in overweight or obese patients.² The study included adult patients with BMI ≥ 30 kg/m² or patients with BMI ≥ 27 kg/m² with dyslipidemia or hypertension. The intervention group received NB32 twice daily for 56 weeks while the control group received placebo. Both groups received instruction for hypocaloric diet (500 kcal/day deficit) and increased physical activity. The primary outcomes were percent weight change and patients having $\geq 5\%$ weight loss at week 28. At 28 weeks, NB32 had a greater mean weight loss compared with placebo (–6.5% vs –1.9%, $P<.001$). Furthermore, this weight loss was maintained at follow-up at week 56 (–6.4% vs –1.2%, $P<.001$). More patients achieved $\geq 5\%$ weight loss with NB32 compared with placebo at week 28 (55.6% vs 17.5%, $P<.001$) and week 56 (50.5% vs 17.1%, $P<.001$). This RCT was limited by diversity in participants (as most were middle-aged, white female patients) and a completion rate of only 54% across all treatment groups.

A 2017 multicenter RCT (n=300) analyzed the effects of 32 mg naltrexone SR/360 mg bupropion SR plus comprehensive lifestyle intervention (NB32+CLI) compared with standard diet and exercise advice (usual care) for 78 weeks on achieving $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ weight loss.³ Adult patients had a BMI 30 to 45 kg/m² or BMI 27 to 45 kg/m² with hyperlipidemia or hypertension. Researchers excluded patient with heart-related disease; type 1 or 2 diabetes

mellitus; or a history of seizures, strokes, or use of opioids. Patients were randomly assigned to either NB32+CLI or usual care with diet and exercise education alone for 26 weeks. After 26 weeks, patients in the usual care group received NB32+CLI. Treatment with NB32+CLI significantly improved weight loss over usual care with a reduction in body weight 9.46% versus 0.94% ($P<.0001$) at 26 weeks. Weight loss persisted through 78 weeks. Significantly more patients on NB32+CLI achieved weight loss of $\geq 5\%$ (84.5% vs 12.2%, $P<.001$) and $\geq 10\%$ (42.3% vs 3.7%, $P<.001$) compared with usual care. Patients in the NB+CLI group had markedly lower triglycerides, waist circumference, glucose, insulin, and a measure of insulin resistance, as well as an increase in high-density lipoprotein cholesterol.

A 2010 multicenter RCT (n=1,742) examined the mean change in body weight for patients taking 16 mg naltrexone SR/360 mg bupropion SR (NB16) or 32 mg naltrexone SR/360 mg bupropion SR (NB32) compared with placebo.⁴ Patients were adults with a BMI 30 to 45 kg/m² or BMI 27 to 45 kg/m² with dyslipidemia or hypertension. Patients with type 1 or type 2 diabetes or previous surgical or device intervention were excluded. All patients received education and instruction for a hypocaloric diet (500 kcal/day deficit) and increased physical activity. They were assigned randomly in a 1:1:1 ratio to NB16, NB32, or placebo groups. The primary outcomes were percent change in body weight at 56 weeks and proportion of patients with 5% or greater decrease in body weight. After 56 weeks, the mean change in body weight was greatest with NB32 (–6.1%, $P<.001$) and NB16 (–5%, $P<.001$) compared with placebo (–1.3%). Sixteen percent of patients in the placebo group had a $\geq 5\%$ decrease in body weight compared with 39% using NB16 ($P<.0001$) and 48% using NB32 ($P<.0001$). The most common side effect in patients treated with the naltrexone–bupropion combination was nausea. The RCT was limited by enrolling healthy population of mostly middle-aged white women and had a completion rate of only 50%. EBP

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References

1. Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis [published correction appears in JAMA. 2016;316(9):995]. *JAMA*. 2016; 315(22):2424–2434. [STEP 1]
2. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)*. 2013; 21(5):935–943. [STEP 2]
3. Halseth A, Shan K, Walsh B, Gilder K, Fujioka K. Method-of-use study of naltrexone sustained release (SR)/bupropion SR on body weight in individuals with obesity. *Obesity (Silver Spring)*. 2017; 25(2):338–345. [STEP 2]
4. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial [published correction appears in Lancet. 2010;376(9750):1392; Lancet. 2010;376(9741):594]. *Lancet*. 2010;376(9741): 595–605. [STEP 2]

Is nitazoxanide effective for the prevention of hepatic encephalopathy?

EVIDENCE-BASED ANSWER

It may find a place. In patients with hepatic encephalopathy, nitazoxanide (NTZ) with lactulose may produce a shorter recovery time than using lactulose alone (**SOR: B**, single randomized controlled trial [RCT]). Compared with treatment with rifaximin, NTZ therapy may increase time in remission (**SOR: C**, single 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 randomized controlled trial (RCT) (n=118) evaluated the safety and adequacy of lactulose plus nitazoxanide (NTZ) versus lactulose with placebo in managing overt hepatic encephalopathy (HE).¹ Patients had liver cirrhosis

(based on laboratory findings, endoscopic results, ultrasound examination, and histopathologic criteria) with overt HE who were admitted to an inpatient unit. Those with elevated serum creatinine, hepatocellular carcinoma, degenerative central nervous system disease, psychiatric illness, or alcohol consumption during the past month were excluded. The intervention group received NTZ 500 mg twice daily and lactulose 30 to 60 mL three times daily to produce 2 to 3 semisoft stools per day, while the control group received just lactulose at same dosing. The primary outcome was total time for reversal of HE using the Clinical Hepatic Encephalopathy Staging Scale (CHESS), which scores hepatic encephalopathy from 0 (normal mental status) to 9 (deep coma) based on alertness, orientation, and ability to talk and respond. The treatment group had a shorter recovery time than patients taking only lactulose (1.8 vs 2.1 days, $P=.03$). Adverse effects included epigastric pain, hepatorenal syndrome, and significantly greater bleeding in the control group compared with the treatment group (37% vs 10%, $P<.01$).

A small RCT (n=60) compared the efficacy of off-label NTZ with rifaximin for the prevention of HE.² Patients included had a mean age of approximately 54 years old and cirrhosis with at least one episode of HE—no active gastrointestinal tract bleeding, no major psychiatric illness, and no renal insufficiency. The treatment group received NTZ 500 mg twice daily for 24 weeks, while the rifaximin group received 550 mg twice daily for 24 weeks, both drugs administered orally or through nasogastric tube if necessary. The primary outcome was the remission rates of HE over the six-month treatment period. After six months, patients in the NTZ group had a significantly greater time in remission compared with the rifaximin group (136 vs 67 days, $P<.01$). Compared with baseline, NTZ showed significantly reduced INR (2.1 vs 1.6, $P<.01$) and increased albumin (2.4 g/dL vs 2.8 g/dL, $P=.03$). Compared with rifaximin, NTZ demonstrated significantly greater reduction in the Child-Pugh score (range 0–15; mean difference [MD] 0.5 vs 0.7, $P=.02$) and decreased serum ammonia (MD 10.4 vs 17.2 $\mu\text{mol/L}$, $P=.045$). Both groups showed a decrease in ammonia and CHESS scores after 24 weeks without any significant difference between the two groups. Side effects in both groups were reported as minor and included GI symptoms, dizziness, and headache, with the only significant difference being a higher incidence of diarrhea in the rifaximin group (13.3% vs 0%, $P=.04$).

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References

1. Glal KAM, Abd-Elsalam SM, Mostafa TM. Nitazoxanide versus rifaximin in preventing the recurrence of hepatic encephalopathy: a randomized double-blind controlled trial. *J Hepatobiliary Pancreat Sci*. 2021; 28(10):812–824. [STEP 2]
2. Abd-Elsalam S, El-Kalla F, Elwan N, et al. A randomized controlled trial comparing nitazoxanide plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *J Clin Gastroenterol*. 2019; 53(3):226–230. [STEP 2]

Is nitrous oxide an effective monotherapy for labor pain?

EVIDENCE-BASED ANSWER

Yes. Nitrous oxide monotherapy is an effective modality for reducing labor pain by as much as 3 to 5 points on a 10-point pain scale compared with placebo, although it is less effective than alternative inhaled therapies (SOR: **A**, systematic review of RCTs and RCTs).

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

A 2012 systematic review of 26 RCTs (N=2,959) compared the efficacy of different inhaled analgesia agents for pain management in labor.¹ The review included spontaneous and induced labor in both nulliparous and multiparous women during various stages of labor. These RCTs compared pain relief outcomes in

patients receiving various concentrations of inhaled nitrous oxide ranging from 50% to 70% versus inhaled flurane analgesics, placebo, no treatment and other nonpharmacological interventions. Primary outcomes included pain intensity, satisfaction with pain relief collected within 48 hours after birth, sense of control in labor, and satisfaction with childbirth experience. The review found flurane derivatives to offer more pain relief in the first stage of labor when compared with nitrous oxide, as measured by lower pain intensity on a 0 to 100 visual analog scale (VAS) (3 trials; N=70; mean difference [MD] 14; 95% CI, 4.4–24) and higher pain relief on a 0 to 100 VAS (2 trials; N=70; MD –16; 95% CI, –27 to –5.8). RCTs evaluating effects of nitrous oxide compared with no treatment or placebo found less pain relief in placebo/no treatment groups (2 trials; N=310, N=509; mean difference [MD] –3.5; 95% CI –3.8 to –3.3). Studies comparing different concentrations of analgesics, different delivery systems, or inhaled analgesics to TENs did not find a statistical difference in outcomes.

A 2017 randomized control trial examined labor pain relief in 120 nulliparous women with use of Entonox inhalation compared with O₂ inhalation.² Patients were in the active phase of labor (cervical dilation of 3–4 cm and effacement of 40%–50%) and randomly assigned to receive inhaled Entonox (50% oxygen, 50% nitrous oxide) or inhaled oxygen alone at each contraction, starting at the onset of contraction pain and stopping with end of contraction pain. Patients were asked to rate their pain severity 0 to 10 with a visual analog scale at the first, second, third, and fourth hour of labor. Compared with placebo group, there was better pain relief in the Entonox group in the first hour (6.0 vs 8.5, $P \leq .001$), second hour (5.4 vs 8.1, $P \leq .001$), third hour (1.3 vs 6.3, $P \leq .001$), and fourth hour (0.28 vs 1.9, $P \leq .001$). Entonox therapy resulted in more nausea compared with oxygen (59% vs 3.3%, $P \leq .001$) as well as decreased duration of first (65 minutes vs 98 minutes, $P \leq .001$) and second stages of labor (44 minutes vs 64 minutes, $P \leq .001$). No significant complications were observed of Entonox use. This study was limited by self-reported pain levels and convenience sampling.

A 2013 RCT of 200 pregnant women examined the effectiveness of nitrous oxide (Entonox) on labor pain and labor delivery time compared with oxygen.³ The RCT included women between 37 and 41 weeks gestation of single fetal pregnancy, without

polyhydramnios, oligohydramnios, or meconium discharge. Patients were randomly assigned to either the trial group (Entonox) or a control group (oxygen). Selected therapy was initiated at start of active phase of labor (cervical dilation 3–4 cm and effacement 40%–50%), with patients self-administering therapy during each contraction at onset of pain and stopping therapy with end of pain. Analysis showed a reduction in the mean duration of active phase with Entonox versus oxygen control (4.1 hours and 5.3 hours, $P=.03$), along with a decrease in mean pain severity during uterine contractions (5.2 and 9.0, $P<.005$). No significant complications were observed of nitrous oxide use, and the most common side effect reported was lethargy (40.1%).

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References

1. Klomp T, van Poppel M, Jones L, Lazet J, Di Nisio M, Lagro-Janssen ALM. Inhaled analgesia for pain management in labour. *Cochrane Database Syst Rev*. 2012; 9:CD009351. [STEP 1]
2. Parsa P, Saeedzadeh N, Roshanaei G, Shobeiri F, Hakemzadeh F. The effect of entonox on labour pain relief among nulliparous women: a randomized controlled trial. *J Clin Diagn Res*. 2017; 11(3):QC08–QC11. [STEP 2]
3. Najefian M, Cheraghi M, Pourmehdi Z, Nejad AD. The effect of nitrous oxide (ENTONOX) on labour pain relief during delivery stages. *Int J Pharm Ther*. 2013; 4(4):242–246. [STEP 2]

Is observation a reasonable management option for toddler's fracture?

EVIDENCE-BASED ANSWER

In children with toddler's fractures, observation may be reasonable for management because no increased risks of fracture-related adverse outcomes were observed and there may be decreased healthcare service utilization associated with observation (SOR: B, systematic review of retrospective cohort studies). In children around two years old who experience a toddler's fracture observation may lead to fewer complications with similar outcomes and patient/family satisfaction when compared with casting (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).

In 2022, a systematic review and meta-analysis of four retrospective cohort studies (N=355) compared the efficacy of immobilization with no immobilization for treatment of toddler's fractures in children.¹ The review defined toddler's fractures as closed, nondisplaced or minimally displaced, nonphyseal, spiral, and oblique fractures of the tibia shaft in children up to six years old. The review excluded reports of patients with pathologic tibial fractures or those caused by a non-trivial injury such as a motor vehicle accident. Patients were predominantly male patients (70.4%) evaluated in orthopedic clinics or emergency departments in pediatric-only hospitals in the United States or Scotland. Patients in the immobilization cohort (N=327) received either circumferential above-knee or below-knee casts, splints, or custom removable devices while those in the no immobilization cohort (N=28) received no intervention. The primary outcome was a composite of fracture-related adverse events (displacement, malunion, angulation, shortening, neurovascular injury, or refracture). Secondary outcomes were the composite of immobilization-related adverse events (skin breakdown, infection, cast breakage, or protracted limping), change in management, and healthcare service utilization. Pooled analyses showed no difference between immobilization versus no immobilization with respect to composite fracture-related

adverse outcomes (4 studies, N=355; risk difference 0; 95% CI, -0.09 to 0.09). Among patients who had fracture immobilization, 8% had an adverse event (most often skin breakdown or infection due to casting); however, this was not statistically significant (4 studies, N=327; absolute risk 0.08; 95% CI, -0.01 to 0.17). Change in management rates did not differ between immobilization and no immobilization cohorts. Regarding healthcare service utilization, immobilization resulted in fewer follow-up radiographs (1 study, n=75; mean difference [MD] 0.69; 95% CI, 0.15–1.2) and about one fewer scheduled outpatient orthopedic visits (1 study, N=75; MD 0.96; 95% CI, 0.24–1.7). No difference was observed in repeat emergency department visits for immobilization when compared with no immobilization. Limitations include lack of data on pain, caregiver satisfaction, and outcomes associated with specific types of immobilization.

A single-center prospective cohort study (n=44) examined the effectiveness of long leg casting for toddler's fracture compared with observation.² Patients had a mean age of 1.9 years old (52% male) with a toddler's fracture diagnosed within two weeks of presenting to a pediatric hospital emergency department. Patients with fracture displacement >2 mm, metabolic bone disease, or suspected nonaccidental trauma were excluded. The intervention group received four weeks treatment of a long leg fiberglass cast applied with the knee in flexion and ankle in neutral dorsiflexion while observed patients were not casted. The primary outcomes were the number of complications and additional visits, and secondary outcomes were radiographic displacement, family-reported outcome scores, and family satisfaction survey results measured at eight weeks postdiagnosis. The casted group experienced more complications than the observation group (4 vs 0; 2 recasted for cast damage and 2 did not tolerate the cast; $P=.01$), but none had skin breakdown. Patients in the cast versus observation group had more additional visits, but the difference was not significant (2 vs 0, $P=.11$). Neither group had radiographic displacement. Family-reported outcome scores improved in both groups over eight weeks and were not significantly different between groups during treatment. Similarly, no significant differences were observed in family satisfaction scores between groups.

EBP

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References

1. Boutin A, Misir A, Boutis K. Management of toddler's fracture: a systematic review with meta-analysis. *Pediatr Emerg Care*. 2022; 38(2):49–57. [STEP 2]
2. Fox J, Enriquez B, Bompadre V, Carlin K, Dales M. Observation versus cast treatment of toddler's fractures. *J Pediatr Orthop*. 2022; 42(5):e480–e485. [STEP 3]

Do statins increase the risk for the development of diabetes?

EVIDENCE-BASED ANSWER

Statin therapy increases the risk of new-onset diabetes mellitus (SOR: **A**, 2 meta-analysis of randomized controlled trials and observational studies). High-intensity statins carry a higher risk of development of new-onset diabetes compared with low-intensity statins (SOR: **B**, meta-analysis of observational studies), with higher risk seen in atorvastatin and rosuvastatin (SOR: **B**, large retrospective 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 meta-analysis of 33 randomized controlled trials (RCTs; N=163,688) examined new-onset diabetes (NODM).¹ Patients had a mean age of 59.9 years old, with 18% to 100% male across the trials. Patients

were included if they had hypercholesterolemia, atherosclerotic cardiovascular disease (ASCVD) risk factors, previous myocardial infarction (MI) or acute coronary syndrome (ACS), coronary heart disease (CHD), congestive heart failure, or valvular heart disease. The intervention group received statin therapy, whereas the control group included usual care or placebo. Follow-up ranged from 104 to 349 weeks. The primary outcome was NODM that was defined as multiple criteria, including adverse events (unspecified), one or two fasting blood glucose measurements >126 mg/dL, positive oral glucose tolerance test, WHO 1999 criteria, and starting a diabetes medication. Statin “intensity” indicated potency of the statin used. Compared with patients who did not take a statin, patients who took any statin were significantly more likely to develop NODM (21 RCTs, N=124,755; risk ratio [RR] 1.09; 95% CI, 1.03–1.16). High-intense statins were significantly associated with a higher risk of NODM compared with low-intensity statin therapy (21 RCTs, N=124,755; RR 1.11; 95% CI, 1.03–1.19; $I^2=0\%$). This study was limited by different definitions of NODM across the trials.

A 2017 meta-analysis of 20 observational studies (N=4,066,854) evaluated the development of diabetes in patients taking statins versus not taking statins.² Patients were adults, with a mean age of 56.9 years old. No other demographic information was provided. Follow-up duration across the studies ranged from 2 to 20 years, with a mean duration of 7.2 years. Studies were included if they had at least 1,000 adult patients followed for at least one year. The primary outcome was NODM that was defined as receiving a diagnosis, taking diabetes medications, self-report, biochemical markers, or a combination of these. Compared with patients who did not take a statin, patients who took any statin were significantly more likely to develop NODM (19 studies, N=4,055,139; RR 1.44; 95% CI, 1.31–1.58). In addition, compared with patients who took low-intensity statins, patients who took the high-intensity statins were more likely to develop NODM: simvastatin (8 studies, N=77,372; RR 1.38; 95% CI, 1.19–1.61), pravastatin (8 studies, N=63,912; RR 1.39; 95% CI, 1.09–1.77), fluvastatin (6 studies, N=7,022; RR 1.39; 95% CI, 1.09–1.77), rosuvastatin (6 studies, N=38,155; RR 1.61; 95% CI, 1.31–1.98), and atorvastatin (7 studies, N=51,121; RR 1.49; 95% CI, 1.31–1.70). This study was limited by broad inclusion criteria and definitions of NODM.

A 2022 multicenter, retrospective cohort study (n=14,605,368) compared risk of NODM in new patients of pitavastatin versus atorvastatin and rosuvastatin.³ Patients were adults (age >18 years old) from 10 hospitals in Korea and used statins for >180 days. Patients were excluded if they had prior exposure to the studied statins or other statins (including simvastatin, pravastatin, lovastatin, or fluvastatin), or an exposure to any oral hypoglycemic agent, glucagon-like peptide-1 (GLP-1) receptor agonist, insulin, or had a serum HbA1c >5.7%. The primary outcome was incidence of NODM 180 days after starting statin therapy. NODM was defined as diagnosis of diabetes using ICD-10, prescription of hypoglycemic agent, GLP-1 receptor agonist, or insulin, and serum HbA1c level >6.5%. Pitavastatin was associated with a significantly lower risk of NODM compared with atorvastatin (hazard ratio [HR] 0.69; 95% CI, 0.54–0.88) or rosuvastatin (HR 0.74; 95% CI, 0.55–0.99). No significant difference in the risk of NODM was noted between atorvastatin and rosuvastatin.

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References

1. Khan S, Rahman H, Okurintemi V, et al. Association of lowering low-density lipoprotein cholesterol with contemporary lipid-lowering therapies and risk of diabetes mellitus: a systematic review and meta-analysis. *J Am Heart Assoc.* 2019; 8:e011581. [STEP 1]
2. Casula M, Mozzanica F, Scotti L, et al. Statin use and risk of new-onset diabetes: a meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis.* 2017(27):396–406. [STEP 1]
3. Seo W, Seo S, Kim Y, et al. Impact of pitavastatin on new-onset diabetes mellitus compared to atorvastatin and rosuvastatin: a distributed network analysis of 10 real-world databases. *Cardiovasc Diabetol.* 2022; 21:82. [STEP 3]

Does erenumab provide better prophylactic treatment than topiramate for patients with migraine headaches?

EVIDENCE-BASED ANSWER

Yes. For episodic and chronic migraine, both topiramate and monoclonal antibodies against the calcitonin gene-related peptide receptor (erenumab, galcanezumab, fremanezumab, and eptinezumab) reduce monthly migraine days (MMDs) compared with placebo, but topiramate has a higher risk of adverse events (SOR: A, meta-analysis of RCTs). Erenumab specifically reduces MMDs more than topiramate with fewer adverse events (SOR: B, systematic review and a single head-to-head RCT).

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A 2020 meta-analysis of 13 RCTs (N=7,557) indirectly compared topiramate and monoclonal antibodies against calcitonin gene-related peptide receptor (CGRPR) for the prophylaxis of episodic migraine.¹ This included testing efficacy and safety of erenumab, galcanezumab, fremanezumab, eptinezumab, and topiramate for 12 to 26 weeks. The trials involved predominately female (5:1) patients 28 to 55 years old diagnosed with episodic migraine and 5 to 12 migraine days per month. Interventions included erenumab 70 to 140 mg subcutaneously monthly and topiramate 50 to 200 mg oral daily. The primary outcomes included frequency of monthly migraine days (MMDs) and adverse events. When each compared with placebo, the monthly migraine days decreased with CGRPR monoclonal antibodies (13 trials, N=3,326; mean difference -1.6 days; 95% CI, -1.9 to -1.2; $I^2=49\%$) and topiramate (4 trials, N=1,032; mean difference -1.1 days;

95% CI, -1.6 to -0.59; $I^2=46\%$) with no difference between the groups (-1.6 vs -1.1 days; $P=.15$). In patients treated with topiramate compared with placebo, a higher risk of cognitive and sensory/pain adverse events was observed (5 studies, N=1,911; risk ratio [RR] 2.2; 95% CI, 1.8–2.6; and 5 studies, N=1,911; RR 8.0; 95% CI, 4–16), while local site reactions were more common with CGRPR monoclonal antibodies than placebo (7 studies, N=4,683; RR 1.6; 95% CI, 1.2–2.1). No difference was observed between the NNT for CGRPR monoclonal antibodies and topiramate (6 vs 7; $P=.39$). The NNH was higher for CGRPR monoclonal antibodies than topiramate (120 vs 9; $P=.005$). Limitations included different end points among trials and differences in inclusion and exclusion criteria.

In 2019, a systematic review of 11 RCT (including a phase 2 and a phase 3 clinical trial) assessed the benefit-risk profile of erenumab relative to propranolol, topiramate, and onabotulinumtoxin A for migraine prophylaxis in 4,992 patients.² Compared with the prior systematic review, eight trials uniquely evaluated patients with chronic migraine while one trial overlapped with the prior meta-analysis. Most patients were female patients (>75%), with an average age of 40 years. Study duration was 12 to 16 weeks for chronic migraines. Interventions of interest were subcutaneous erenumab 70 or 140 mg monthly and oral topiramate 100 mg daily. The primary outcome was risk benefit of prophylactic therapy for migraine as measured by NNT and NNH. All prophylactic migraine treatments were more likely to help than harm. Calculations were not pooled. For chronic migraine treatment with topiramate the NNT was four (1 trial, n=59; 95% CI, 3–10) and 13 (2 trials, n=306; 95% CI not reported), NNH 13 (1 trial, n=59; 95% CI not reported), and 21 (2 trials, n=306; 95% CI, not reported). For chronic migraine, one trial showed erenumab 140 mg (n=468) and 70 mg (n=469) had an NNT of six (95% CI, 4–12) and seven (95% CI, 5–13) and an NNH of 250 and 1,000 (95% CIs not reported). The medications were not compared head-to-head.

A 2022 double-blind and double-dummy RCT with 777 patients in Germany measured the reduction in MMDs from baseline between erenumab and topiramate and the percent of patients who discontinued treatment because of AEs.³ Patients were 18 to 65 years old with four or more MMDs who had not been treated with topiramate or a CGRPR monoclonal antibody. Patients were

randomly assigned to subcutaneous erenumab plus oral placebo or oral topiramate plus subcutaneous placebo. More patients achieved >50% reduction in MMDs from baseline with erenumab compared with topiramate (55% vs 31%; odds ratio [OR] 2.8; 95% CI, 2.1–3.7). Fewer patients discontinued erenumab than topiramate because of adverse side effects (11% vs 39%; OR 0.19; 95% CI, 0.13–0.27). A limitation of this study was that they did not include a placebo group to judge placebo and nocebo effects. Another limitation was the possible partial unblinding because of the typical side effects of topiramate.

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References

1. Overeem LH, Raffaelli B, Mecklenburg J, Kelderman T, Neeb L, Reuter U. Indirect comparison of topiramate and monoclonal antibodies against CGRP or its receptor for the prophylaxis of episodic migraine: a systematic review with meta-analysis. *CNS Drugs*. 2021; 35(8):805–820. [STEP 1]
2. Vo P, Wen S, Martel MJ, Mitsikostas D, Reuter U, Klatt J. Benefit-risk assessment of erenumab and current migraine prophylactic treatments using the likelihood of being helped or harmed. *Cephalalgia*. 2019; 39(5):608–616. [STEP 1]
3. Reuter U, Ehrlich M, Gendolla A, et al. Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. *Cephalalgia*. 2022; 42(2):108–118. [STEP 2]

In patients with elevated blood pressure, does resistance training reduce blood pressure?

EVIDENCE-BASED ANSWER

Patients with elevated blood pressure who perform regular resistance training experience small decreases in systolic and diastolic blood pressures compared with patients who do not perform additional physical training beyond normal daily activity (SOR: **A**, meta-analysis of RCTs).

Compared with steady-state treadmill exercise or controls, patients participating in a supervised, resistance training regimen may have a significant decrease in systolic blood pressures (SOR: **C**, small RCT).

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In 2021, a meta-analysis of 13 randomized controlled trials (N=417) compared resistance training (RT) with no training on changes in blood pressure (BP) in adults with prehypertension and hypertension.¹ The review included trials of between 8 and 16 weeks of duration (mean 12 weeks). Approximately 70% of patients were older than 60 years old. Patients with cardiovascular risk factors (eg, overweight, obesity, prediabetes, and elevated cholesterol) and those with known cardiometabolic disease (eg, coronary heart disease, type 2 diabetes, and heart failure) were included. Studies combining RT with other types of training (eg, aerobic training) and lifestyle interventions (eg, nutrition, psychological interventions) were excluded. Most studies included patients taking hypertensive medications. Patients assigned to perform RT did so two to 3 times per week, implementing between 7 and 15 total exercises per session, with 6 to 25 repetitions per exercise, while those assigned to the control group did not perform additional physical training beyond normal daily activity. Studies evaluated the effects of RT on both systolic blood pressure (SBP) and diastolic blood pressure (DBP). RT decreased SBP (13 trials, N=417; mean difference [MD] –6.2 mmHg; 95% CI, –8.3 to –4.0) and DBP (13 trials, N=417; MD –3.7 mmHg, 95%, CI –5.2 to –2.2). Elderly patients demonstrated similar reductions when compared with controls in SBP (9 trials, N=302; MD –5.7 mmHg; 95% CI –8.1 to –3.3) and DBP (9 trials, N=302; MD –3.3 mmHg; 95% CI –4.7 to –1.8). Limitations of the review included heterogenous blood pressure

measurements (office vs 24-h BP) and the type, frequency, and duration of RT across studies.

A small 2018 RCT compared the effects of high-velocity circuit resistance training (HVCRT) and steady-state treadmill training (TM) on blood pressure in 30 patients.² The study included mostly female patients older than 65 years old and mean body weight of 81 kg. Approximately 78% of the HVCRT group met cardiometabolic syndrome criteria for elevated BP (systolic blood pressure > 130 mmHg and/or diastolic blood pressure > 85 mmHg) compared with 25% in the TM group and 43% of controls. Patients were excluded if they regularly participated in structured exercise programs or had any uncontrolled disease processes (including cardiovascular disease). In the experimental protocols, patients participated in a supervised, 12-week exercise regimen three days per week, and those in the control group did not alter their physical activity. Patients in the HVCRT group completed 11 exercises with 12 repetitions of each exercise with a two-second controlled eccentric phase and self-directed rest intervals. They completed the exercises in the same order each time: chest press, leg press, latissimus dorsi pull-down, seated rows, hip abduction, elbow extension, plantar flexion, and elbow flexion. In the TM group, patients first underwent a three-week conditioning period in which they walked on the treadmill until they were able to complete a full 35 minutes of exercise. During weeks 4 to 12, patients continued 35-minute workouts three days/week and increased intensity until they were within two bpm of their target heart rate (55% of heart rate reserve using the Karvonen formula for maximum heart rate). Patients in the HVCRT group had greater reduction in systolic blood pressure compared with controls (mean difference -16 mmHg; 95% CI, -25 to -6.4) and TM (MD -10 mmHg; 95% CI, -20 to -0.4). In addition, diastolic blood pressure improved in the HVCRT group compared with controls (MD -10 mmHg; 95% CI, -7.7 to -2.9), but not compared with the TM group. Limitations of this study include lack of blinding for physiologic measurements, lack of intention-to-treat analysis, and small size. **EBP**

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References

1. Abrahin O, Moraes-Ferreira R, Cortinhas-Alves EA, Guerreiro JF. Is resistance training alone an antihypertensive therapy? A meta-analysis [published correction appears in *J Hum Hypertens*. 2021 Aug 5. *J Hum Hypertens*. 2021; 35(9):769–775. **[STEP 1]**
2. Roberson KB, Potiaumpai M, Widdowson K, et al. Effects of high-velocity circuit resistance and treadmill training on cardiometabolic risk, blood markers, and quality of life in older adults. *Appl Physiol Nutr Metab*. 2018; 43(8):822–832. **[STEP 3]**

In adult patients with gastroesophageal reflux disease, is twice-daily proton pump inhibitor dosing more effective than once-daily dosing in relieving symptoms?

EVIDENCE-BASED ANSWER

Maybe not. In adults with refractory gastroesophageal reflux disease, twice-daily dosing of rabeprazole leads to only minor and inconsistent improvements in symptoms compared with once-daily rabeprazole. It is not known how other proton pump inhibitors, potentially with different pharmacokinetics, would perform (SOR: **C**, randomized controlled trials with inconsistent results).

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

A double-blinded randomized controlled trial (RCT) completed in 2012 (n=337) assessed the efficacy of once-daily versus twice-daily rabeprazole over the course of eight weeks of treatment.¹ Patients were adults (mean age 65 years old) who had persistent symptoms and esophagogastroduodenoscopy-proven reflux esophagitis

despite standard proton pump inhibitor (PPI) therapy (rabeprazole 10 mg daily) for at least eight weeks. Excluded patients had Barrett's esophagus, active peptic ulcer disease, or had undergone treatment for *Helicobacter pylori* infection in the previous six months. Patients were randomized to one of three rabeprazole regimens: 10 mg twice daily (n=111), 20 mg once daily (n=113), or 20 mg twice daily (n=113). Endoscopic healing rate was the primary outcome, and heartburn symptom improvement was reported as a secondary outcome. Heartburn symptoms were rated on a four-point scale: none, mild (awareness only), moderate (interfering with normal activities), or severe (resulting in inability to perform normal activities). Resolution of heartburn was defined as a rating of none. Comparing the regimens with equivalent total daily dose of 20 mg, the 10 mg twice-daily group had a significantly greater rate of heartburn resolution compared with the 20 mg once-daily group at seven weeks (numerical data not reported; $P<.025$). The higher total dose group taking 20 mg twice-daily also had significantly greater rates of heartburn resolution compared with the 20 mg once-daily group at seven weeks (numerical data not reported; $P<.025$). This improvement in heartburn resolution persisted at eight weeks only in the 20 mg twice-daily group compared with the 10 mg twice-daily and 20 mg once-daily groups (80% vs 74% and 56%, $P<.025$). No significant difference was observed between the 10 mg twice-daily and 20 mg once-daily groups at eight weeks ($P>.05$). Rates of adverse drug reactions were reported to be similar between the 10 mg twice-daily and 20 mg once-daily groups but higher in the 20 mg twice-daily group. This was not defined further except to note a transient increase of thyroid-stimulating hormone occurring in up to 7% of participants and more common with twice-daily dosing. Because only one PPI was evaluated, it is unknown how other PPIs, potentially with different pharmacokinetics, would perform.

In 2016, a multicenter RCT (n=78) compared the efficacy of once-daily and twice-daily proton pump inhibitor (PPI) therapy at higher-than-standard dose for the treatment of refractory gastroesophageal reflux disease.² The mean age of patients was 63 years old, and all had persistent symptoms despite treatment of at least four weeks with standard PPI dosing. Patients with malignancy, active peptic ulcer disease, previous gastrointestinal surgery, treatment with double-dose PPI in the past four weeks, or treatment for *Helicobacter pylori* in the previous six months were excluded. Researchers randomly assigned patients to rabeprazole 20 mg daily

in the morning (n=39) or rabeprazole 10 mg twice daily (n=39). At baseline and at four and eight weeks of treatment, patients completed the self-administered Global Overall Symptoms (GOS) questionnaire to assess upper gastrointestinal symptoms including epigastric pain, heartburn, regurgitation, bloating, nausea, excessive belching, postprandial fullness, and early satiety; each rated on a 1 (no problem) to 7 (very severe problem) scale. All patients scored four or more points for at least one symptom at baseline. Symptom improvement was defined as achieving a score of two or less for each symptom. The once-daily and twice-daily groups had similar rates of symptom improvement after eight weeks of treatment (42% and 49%, respectively; $P=.384$). For individual symptoms at eight weeks, once-daily rabeprazole did not significantly improve epigastric pain (3.2–2.1; $P>.05$) or postprandial fullness scores (2.5–1.8; $P>.05$) compared with baseline; however, the other six symptom scores significantly improved by a minimum of 0.9 points and a maximum of 1.5 points ($P<.05$ for each). In comparison, twice-daily rabeprazole significantly improved all eight symptom scores by a minimum of 0.5 points and a maximum of 1.7 points from baseline to eight weeks ($P<.05$ for each). Adverse drug reactions were reported in only two patients, lower extremity edema and nausea, but group assignment of these two patients was not reported. Again, it is unknown how other PPIs, potentially with different pharmacokinetics, would perform.

EBP

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References

1. Kinoshita Y, Hongo M. Efficacy of twice-daily rabeprazole for reflux esophagitis patients refractory to standard once-daily administration of PPI: the Japan-based twice study. *Am J Gastroenterol.* 2012; 107(4):522–530. [STEP 2]
2. Mizuki A, Tatemichi M, Sakakibara T, et al. A multicenter, randomized, open-label trial: efficacy of once-daily versus twice-daily double-dose rabeprazole on refractory gastroesophageal reflux disease-related symptoms and quality of life. *Curr Ther Res.* 2016; 79:1–7. [STEP 2]

Is acupuncture an effective treatment for diabetic gastroparesis?

EVIDENCE-BASED ANSWER

Traditional Chinese acupuncture may help with symptoms of diabetic gastroparesis as compared with motility agents after four to 12 weeks of therapy. Traditional Chinese acupuncture along with motility agents may be more effective for symptoms of diabetic gastroparesis than motility agents alone at four to 12 weeks (SOR: **B**, systematic review and meta-analysis of low-quality randomized controlled trials [RCTs]). Acupuncture may specifically improve nausea, vomiting, and early satiety caused by gastroparesis (SOR: **B**, meta-analysis of multiple low-quality RCTs). It is unclear whether acupuncture improves gastric emptying time (no SOR given, conflicting meta-analyses of low-quality RCTs).

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A 2018 meta-analysis of 32 randomized controlled trials (RCTs) (N=2,601) evaluated the effectiveness of traditional Chinese acupuncture for gastroparesis.¹ The trials included adult patients 30 to 75 years old with a diagnosis of diabetes (except 1 trial investigating postsurgical gastroparesis), cardinal symptoms of gastroparesis, and confirmed delayed gastric emptying time through radio imaging studies. Traditional Chinese acupuncture was compared with sham acupuncture, acupuncture with motility agents, or motility agents alone. The acupuncture groups consisted of electrical or manual therapy using variously defined protocols for an average of 11 points per session for an average of 28 sessions. Motility agents used included mosapride (15–30 mg daily), cisapride (5 mg daily), domperidone (10–30 mg daily), or the antihistamine cimetidine (10 mg TID). Before and after four to 12 weeks of treatment, symptoms were measured using

a validated scale (a 0–3 scale, 3=severe or a 0–4 scale such as Gastroparesis Cardinal Symptom Index, 4=very severe) and evaluated for a 25% or greater reduction in symptom severity. Patient symptom scores did not differ between sham and traditional acupuncture at 12 weeks. Compared with motility agents, traditional acupuncture had a higher success rate of treating gastroparesis after four to 12 weeks (12 trials; N=963; risk ratio [RR] 1.3; 95% CI, 1.2–1.3). Compared with motility agents alone, treatment with acupuncture and motility agents resulted in greater symptom improvement at four to 12 weeks (17 studies; N=1,404; RR 1.2; 95% CI, 1.2–1.3). Limitations included a high risk for allocation bias, reporting bias, and the lack of ability to blind participants. In addition, nine of the 31 studies investigating diabetic gastroparesis did not specify their diagnostic criteria for diabetes.

A 2013 meta-analysis of 14 RCTs (N=914) examined the efficacy of acupuncture for the treatment of nonorganic dyspepsia suggestive of gastroparesis.² The trials included diabetic patients of all ages with dyspeptic symptoms but no ulceration or gastric outlet obstruction on imaging. Patients received either acupuncture/electro acupuncture or sham acupuncture or standard therapy with prokinetic agents. Studies included were those in which the main intervention was acupuncture combined with acupuncture-related assistant techniques performed two to seven times weekly. Studies of moxibustion or acupuncture combined with Chinese *materia medica* were excluded due to likely confounding results. Outcomes measured during a 14-day to 30-day intervention period were patient-reported improvement of total dyspeptic symptoms, patient-reported improvement in a single dyspeptic symptom, and effect of acupuncture on gastric emptying by scintigraphy or imaging with radio-opaque markers. Acupuncture improved total dyspeptic symptoms compared with either domperidone, cisapride, mosapride, or sham electroacupuncture (8 trials, N=521; standardized mean difference [SMD] –1.1; 95% CI, –1.7 to –0.52). Specific dyspeptic symptoms studied included nausea and vomiting (5 trials, N=271; mean score [MS] –0.44; 95% CI, –0.57 to –0.32), early satiety/loss of appetite (6 trials, N=372; mean difference [MD] –0.24; 95% CI, –0.39 to –0.09), and stomach fullness/bloating (6 trials, N=372; MD –0.41; 95% CI, –0.61 to –0.21). The effect of acupuncture on dyspeptic symptoms was scored into three levels:

significant improvement, improvement, and no improvement. Each level had an effect index of >75%, >25%, and <25%, respectively. Seven trials observed the effect of acupuncture on gastric emptying and found mixed results. Limitations include a high risk of selection bias, detection bias, attrition bias, and publication bias.

A 2022 meta-analysis of 59 RCTs (N=4,373) compared the efficacy of traditional Chinese acupuncture therapies in treating diabetic gastroparesis.³ Patients included were diagnosed with diabetic gastroparesis on the basis of symptoms and abnormal physiological test results, such as abnormal gastric motor function on electrogastric examination and delayed gastric emptying on scintillation scan. Patients with other types of gastroparesis were excluded. Treatment groups received one or more acupuncture therapies (eg, acupuncture, massage, moxibustion therapy alone or in combination) combined with conventional Western medicine treatment. Most studies had one month of treatment course with patients receiving one or three sessions per day. The control groups received standard therapies including gastric motility drugs, hypoglycemic drugs, and health education. The primary outcome of the study included gastric-emptying rate, gastric dynamic/secretion elements and effectiveness rate while the secondary outcome was quality-of-life score, fasting blood glucose, two-hour postprandial blood glucose, and HbA1c level. Compared with conventional therapies, combined treatment with acupuncture and conventional therapies improved overall gastric emptying effectiveness (42 trials, N= 3,394; RR 1.3; 95% CI, 1.2–1.3) measured by solid gastric emptying by radio-opaque markers and gastroparesis symptoms (13 trials, N=1,020; RR 1.2; 95% CI, 1.2–1.3). Limitations included the inability to blind the patients to therapies and inclusion of different acupoint therapies. **EBP**

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The authors declare no conflicts of interest.

References

1. Kim KH, Lee MS, Choi TY, Kim TH. Acupuncture for symptomatic gastroparesis. *Cochrane Database Syst Rev*. 2018; 12(12):CD009676. [STEP 1]
2. Yang M, Li X, Liu S, et al. Meta-analysis of acupuncture for relieving non-organic dyspeptic symptoms suggestive of diabetic gastroparesis. *BMC Complement Altern Med*. 2013;13:311. [STEP 1]
3. Li X, Yan Z, Xia J, et al. Traditional Chinese acupoint massage, acupuncture, and moxibustion for people with diabetic gastroparesis: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2022;101(48):e32058. [STEP 1]

Is acupuncture combined with usual medical care more effective than usual medical care alone for the treatment of knee osteoarthritis pain?

EVIDENCE-BASED ANSWER

Acupuncture in addition to usual medical care improves pain, stiffness, and physical function in patients with knee osteoarthritis as compared with usual care alone. There is no reported benefit on quality of life (SOR: **B**, 2 moderate-quality randomized control trials).

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

A 2012 three-armed, single-blinded, randomized control trial (RCT) (n=120) compared acupuncture with pharmacological treatment, sham acupuncture with pharmacological treatment, and pharmacological treatment alone in the treatment of knee osteoarthritis (OA).¹ All patients had pain for greater than three months and had a diagnosis of knee OA based on the American

TABLE. WOMAC index and visual analog scale (VAS) pain scores for treatment of knee OA: acupuncture versus sham acupuncture and pharmacology treatment

Subscore	Acupuncture group vs Sham group ^a	Acupuncture group vs pharmacologic treatment only group ^a
Week 8		
WOMAC Pain	61 vs 117	61 vs 132
WOMAC Stiffness	13 vs 33	13 vs 34
WOMAC Physical Function	267 vs 504	267 vs 579
VAS Pain	15 vs 36	15 vs 40
Week 12		
WOMAC Pain	78 vs 145	78 vs 154
WOMAC Stiffness	15 vs 40	15 vs 39
WOMAC Physical Function	322 vs 603	322 vs 653
VAS Pain	20 vs 43	20 vs 46

^a $P < .0005$ for all comparisons. WOMAC Pain scale 0 to 500; WOMAC Stiffness scale 0 to 200; WOMAC Physical Function scale 0 to 1,700; VAS pain scale 0 to 100.

College of Rheumatology criteria and a Kellgren-Lawrence (radiologic criteria) score of at least two. Researchers excluded patients with intra-articular injections in the past three months, oral steroid or antiplatelet drug use, and history of gastrointestinal bleed. The primary outcome measure was the Western Ontario and McMaster Universities Arthritis (WOMAC) index version VA3.1 (score 0–2,400) and its three subscales (pain [0–500], stiffness [0–200], and physical function [0–1,700]) at four, eight, and 12 weeks. The WOMAC index is a validated knee and hip OA assessment tool with a higher score meaning more severe impairments. Secondary outcomes included visual analog pain scale (VAS) score (scale 0–100) and a SF-36v2 health assessment, which is a validated quality-of-life assessment. Patients (mean age 62 years old) were randomized into the three groups. Each group received 60 mg of etoricoxib once daily for 60 days. Patients in the acupuncture arm received acupuncture treatment following a standardized protocol biweekly for eight weeks. The sham acupuncture group received treatment with retractable needles following the same standardized treatment protocol and frequency as the acupuncture group. Week 8 and 12 WOMAC scores were improved in the acupuncture group compared with the sham group and pharmacologic-only group for pain, stiffness, and physical function (**TABLE**). VAS scores were improved in the acupuncture group

compared with the sham group and the pharmacologic group at eight and 12 weeks. No difference was observed in quality-of-life assessment on the SF36v2 between groups at eight weeks. Limitations included short duration of follow-up of participants and an inability to blind acupuncturist.

A 2004 RCT with blinded evaluation ($n=97$) compared acupuncture with diclofenac and sham acupuncture with diclofenac for the treatment of pain due to knee OA.² Patients had to be at least 45 years old with pain in one or both knees for at least three months, clinically diagnosed OA based on American College of Rheumatology criteria and at least grade I OA according to the Ahlback classification (radiologic criteria). Exclusion criteria were previous treatment with acupuncture, contraindication to diclofenac, inflammatory, metabolic, or neuropathic arthropathies, severe concomitant illnesses that might interfere with the clinical evaluation of the patient, severe or generalized dermatopathy, pregnancy, or existing treatment with antineoplastic, corticoid, or immunosuppressive drugs. The primary outcomes were the WOMAC index and its three subscales, pain in the knee on a VAS (0–100), dosage of diclofenac accumulated, and the profile of quality of life in the chronically ill (PQLC) instrument (scores from 0–4 in domains of physical capability, physiological function, negative mood, social functioning, and social well-being with higher score meaning higher quality of life). Patients (mean 67 years

old) in both the true acupuncture and sham acupuncture groups received a bag of 21 tablets of 50 mg diclofenac for the week with instruction to take the medication every eight hours and to reduce the dose if symptoms improved. Patients with risk factors received gastroprotective drugs. Patients in the true acupuncture group received treatment following a standardized treatment protocol weekly for 12 weeks. The placebo acupuncture treatment group received treatment from the same specialist with retractable needles following the same treatment protocol and frequency. The WOMAC index used in this study (range 0–96) was reduced in the true acupuncture group compared with the control group overall (mean difference [MD] 24; 95% CI, 15–33), as well as for the subscales of pain (range 0–20) (MD 4.7; 95% CI, 2.9–6.5), stiffness (range 0–8) (MD 1.7; 95% CI, 0.8–2.5), and function (range 0–68) (MD 18; 95% CI, 11–24). The 0 to 100 VAS pain score was also significantly improved in the acupuncture group compared with control (MD 27; 95% CI, 19–35). The total number of diclofenac tablets taken in the true acupuncture group compared with the placebo acupuncture group was reduced by an average of 54 tablets (85 vs 139, $P<.001$). No difference was observed in the PQLC instrument between the two groups. Limitations included short duration of the study and inability to confirm blinding of the participants.

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References

1. Mavrommatis CI, Argyra E, Vadalouka A, et al. Acupuncture as an adjunctive therapy to pharmacological treatment in patients with chronic pain due to osteoarthritis of the knee: a 3-armed, randomized, placebo-controlled trial. *Pain*. 2012; 153(8):1720–1726. [STEP 2]
2. Vas J, Méndez C, Perea-Milla E, et al. Acupuncture as a complementary therapy to the pharmacological treatment of osteoarthritis of the knee: randomized controlled trial. *BMJ*. 2004; 329(7476):1216. [STEP 2]

Is viscosupplementation more effective at controlling pain than steroid injections for adult patients with glenohumeral osteoarthritis?

EVIDENCE-BASED ANSWER

For glenohumeral injection, viscosupplementation and corticosteroid injections similarly decrease pain at three and likely at six months (SOR: **B**, meta-analysis of randomized controlled trials [RCTs] and observational studies and a small, contradictory 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 meta-analysis of 15 studies (N=1,594), consisting of five randomized controlled trials (RCTs), seven cohort studies and three case series, investigated pain control with intra-articular injections of hyaluronic acid (HA) for primary glenohumeral osteoarthritis.¹ All patients were adults at 18 years old or older, with 27%–76% male. HA doses ranged from 2 mL to 8 mL, and frequency ranged from one dose to three weekly doses; for the comparison group, a one-time injection of betamethasone with marcadine or three-weekly injections of methylprednisolone was used. Studies were excluded if they did not report a mean change in the visual analog scale (VAS) score from baseline, did not have HA as an intervention of study, or were literature reviews. The outcome included VAS scores for pain (0–100 mm, higher score indicating more severe pain). Compared with baseline, intra-articular HA significantly reduced pain at three months (8 studies, N=975; mean difference [MD] 26.2 mm; 95% CI, 22.0–30.3 mm) and six months (8 studies, N=975; MD 29.5 mm; 95% CI, 25.5–33.4 mm). No significant difference was

observed between the HA and corticosteroid injection groups at six months (2 studies, N=354; data not provided). The difference between the two groups at three months was not provided. Limitations included lack of standardization of HA and corticosteroid treatment administration and technique.

A 2022 single blinded RCT (n=77) compared HA injection with steroid injection for pain relief with primary glenohumeral osteoarthritis (OA).² Patients were adults with the age range of 57 to 88 years old (mean 72), with 96% female. Patients were included if they had a baseline pain score of at least three on a 0 to 10 cm VAS, attempted conservative treatment for at least three months, and had never had shoulder surgery on the affected shoulder. Excluded were patients who had previous viscosupplementation, complete rotator cuff injuries, corticosteroid use in the prior two months, taking immunosuppressive medications or anticoagulants, neurological injury to the affected limb, or cognitive deficits. Before treatment, patients were categorized as mild (19%), moderate (37%), or severe (44%) arthrosis by Samilson and Prieto classification (based on radiographic findings). Patients were treated either with a single intra-articular injection of 6 mL of HA (n=41) or a single intra-articular injection of 20 mg triamcinolone diluted in saline (n=36), all using ultrasound guided posterior approach. Patients were followed with VAS self-reports at one week and then again at one, three, and six months. Among those with severe OA at baseline, decreases in VAS scores were noted in both treatment groups at three months with no statistical comparison provided, and the decrease in VAS was sustained at six months only in the HA group (HA, 8.6 at baseline, 8.0 at 1 week, 7.5 at 1 month, 7.4 at 3 months,

and 7.2 at 6 months vs triamcinolone, 9.1 at baseline, 6.5 at 1 week, 6.0 at 1 month, 7.0 at 3 months, and 8.9 at 6 months; statistical comparisons between the 2 groups not provided). The same trend was noted among those with either mild or moderate OA at baseline, categorized together as “nonsevere” (HA, 8.1 at baseline, 7.0 at 1 week, 5.0 at 1 month, 5.0 at 3 months, and 4.9 at 6 months vs triamcinolone, 8.3 at baseline, 4.8 at 1 week, 4.1 at 1 month, 6.2 at 3 months, and 7.8 at 6 months; statistical comparisons between the 2 groups not provided). This study was limited by lack of statistical analysis and lack of blinding of the physician and investigators. **EBP**

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References

1. Zhang B, Thayaparan A, Horner N, Bedi A, Alolabi B, Khan M. Outcomes of hyaluronic acid injections for glenohumeral osteoarthritis: a systematic review and meta-analysis. *J Shoulder Elbow Surg.* 2019; 28(3):596–606. [STEP 2]
2. Tortato S, Pochini AC, Andreoli CV, et al. Hyal G-F 20 versus triamcinolone in the treatment of primary shoulder osteoarthritis. Randomized trial. *Acta Orthop Bras.* 2022; 30(1):E244410. [STEP 3]

Does topical NSAID use in adults increase the risk of gastrointestinal bleeding compared to oral NSAID use?

EVIDENCE-BASED ANSWER

Yes. When used for the treatment of knee osteoarthritis, topical nonsteroidal anti-inflammatory drugs (NSAIDs) have a lower risk of composite adverse gastrointestinal events, including bleeding, compared with oral NSAIDs (SOR: **A**, network meta-analysis of randomized controlled trials and cohort trials).

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

A 2021 network meta-analysis of 122 randomized controlled trials (RCTs) and two propensity score-matched cohort studies (N=47,113) compared the efficacy and safety of pharmacologic treatment, including topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs) for knee osteoarthritis (OA).¹ Seven of the studies compared topical NSAIDs, such as diclofenac gel, with oral NSAIDs. Patients were adults diagnosed with knee OA who participated in a nearly four-week trial. Outcomes included pain relief, functional improvement, risk of GI adverse effects (AEs, such as dyspepsia, abdominal pain, vomiting, heartburn, bleeding ulcer, rectal bleeding, and melena), risk of cardiovascular AEs, and risk of withdrawal due to AEs. The meta-analysis compared the efficacy and safety between topical NSAIDs, acetaminophen, or oral NSAIDs. The risk of GI AEs was lower in the topical NSAID group than in the oral NSAID group (79 RCTs, N=5,869; relative risk [RR] 0.46; 95% credible interval, 0.34–0.6). In the cohort studies, the primary outcome of propensity score-matched cohort studies comparing topical NSAIDs with acetaminophen or oral NSAIDs was all-cause mortality with secondary outcomes of significant CV disease, venous thromboembolism, and GI bleeding in one year. Topical NSAIDs showed a lower risk of GI bleeding at one-year follow-up (2 studies, n=not reported; hazard ratio [HR] 0.71; 95% CI, 0.51–1.0).

A 2021 retrospective database analysis from Japan (n=180,371) evaluated the risk of GI events and medical costs associated with NSAID use in patients with OA alone or with chronic low back pain.² Most of the patients

identified were adults between 50 and 60 years (33% of study patients) who were not prescribed analgesics in the prior six months. Patients were followed for a median of 857 days. Patients prescribed NSAIDs in any formulation as first-line therapy had an incidence rate of GI-related events of 9.97 per 10,000 person-years (95% CI, 8.9–11). Gastric ulcers with or without bleeding, duodenal ulcers with or without bleeding, and acute hemorrhagic gastritis were GI-related events identified. The incident rate of GI-related events for those with underlying GI comorbidities was 12 per 10,000 person-years (95% CI, 9.8–19). After adjusting covariates, the incident rate for topical NSAID (patches, other transdermal, or suppository) users was lower than that of oral NSAID users (RR 0.75; 95% CI, 0.38–1.47). Those older than 60 years had a higher risk of developing GI events after NSAID treatment (oral or topical) compared with younger patients. Longer duration and more consistent NSAID use, both oral and topical (defined as used >70% of supplied days), increased the risk of GI events (19.38 per 10,000 person-years; 95% CI, 14.2–24.5). The study's limitations included limited data availability for >65 years old and no data for the elderly >75 years old.

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References

1. Zeng C, Doherty M, Persson MSM, et al. Comparative efficacy and safety of acetaminophen, topical and oral nonsteroidal anti-inflammatory drugs for knee osteoarthritis: evidence from a network meta-analysis of randomized controlled trials and real-world data. *Osteoarthritis Cartilage*. 2021; 29(9):1242–1251. [STEP 1]
2. Kikuchi S, Togo K, Ebata N, et al. A retrospective database study of gastrointestinal events and medical costs associated with nonsteroidal anti-inflammatory drugs in Japanese patients of working age with osteoarthritis and chronic low back pain. *Pain Med*. 2021; 22(5):1029–1038. [STEP 4]