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EVIDENCE-BASED PRACTICE

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FPIN
Family Physicians Inquiries Network

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EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

EDITORIAL

IN DEPTH

DIVING FOR PURLs

HELPDESK ANSWERS

SPOTLIGHT ON PHARMACY

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STATEMENT OF PURPOSE

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

EDITORIAL POLICY

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DISCLOSURE

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Implausibly prolific

Looking back over my FPIN publishing record, I puff up with pride when noting that my resident co-authors and I have produced 3 to 4 publications a year for the last 10 years. Sure, it is a lot of work, especially near the end of the academic year, when resident authors suddenly become motivated. But the rewards are great—collaboration with eager learners, investigating fascinating questions, and probing the edge of medical knowledge. I would do more of it if I just had more time.

But this is a tiny publication rate in some rarefied circles. I have always regarded with a bit of envy those authors who publish substantially more. How, I wonder, can they do it?

To find out, a group of researchers[1] evaluated the Scopus database to identify authors who had published 72 papers or more in any year from 2000 to 2016. That's a paper every five days! The researchers noted that this rate of production might be considered "implausibly prolific." But they found over 9,000 people who had managed to do it. Most (86%) of the authors were publishing in physics, where teams of nearly a 1,000 researchers are common (think Large Hadron Collider). They then culled all the Chinese or Korean authors, where the Scopus database has translational ambiguity problems. That left them with 265 hyperprolific authors outside of physics. Of these, 101 had published in medicine. The highest number (50) worked in the United States. Five worked at Harvard.

The researchers tried to contact all 265 hyperprolific medical authors, and 81 replied, the rest likely being too busy. These authors reported valuing hard work, loving research, enjoying mentoring, leading research teams, working in multiple areas in interest, and sleeping only a few hours per night.

But there were darker associations than just sleep loss. About half did not claim to be accountable for all aspects of all their work. One third stated they were not involved in the research design of all their work. One third stated they did not help with drafting all their papers. A smaller fraction (11%) had not approved the final version in all papers.

Well, if that's how it is done, maybe I should not be envious. I want a deeper sense of ownership (and hope that you do too).

Jon O. Neher

DOI 10.1097/EBP.0000000000001768

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Does close outpatient follow-up after discharge from the hospital reduce readmission rates?

EVIDENCE-BASED ANSWER

Close outpatient follow-up after discharge, with either a general practitioner or a specialist, is associated with decreased readmission rates among patients admitted to general medical floors with cardiac conditions such as non-ST–elevation myocardial infarction and heart failure (SOR: **B**, 2 retrospective cohort studies). Follow-up with the same physician who treated the patient in the hospital may be associated with lower readmission rates than follow-up with a different physician (SOR: **B**, 1 retrospective cohort study).

DOI 10.1097/EBP.0000000000001530

A 2018 retrospective cohort study (N=28,848) examined whether early follow-up appointments after discharge reduced hospital readmission rates for patients with heart failure (HF) in France. Patients included in this paper were at least 65 years old and admitted for HF. Patients were excluded if they were discharged to nursing homes, rehabilitation centers, or psychiatric facilities; were missing resident information; or had a known history of advanced disease (New York Heart Association class IV). The rate of readmission at one month was assessed when follow-up occurred with a general practitioner or specialist (cardiologist) within one week from time of discharge. Close follow-up with a general practitioner reduced readmission rates (odds ratio [OR] 0.51; 95% CI, 0.27–0.98) compared with late or no follow-up. Close follow-up with a specialist practitioner had similar effects on readmission rates (OR 0.38; 95% CI, 0.15–0.96). This paper was limited by selection bias with socioeconomic and rural versus urban residence potentially affecting accessibility of follow-up care.

A 2010 retrospective cohort study (N=18,585) examined the association between close physician follow-up and readmission rates among non-ST–elevation myocardial infarction (NSTEMI) and patients with HF in Taiwan.[2] All patients were adults with a first hospital admission for the primary diagnosis of NSTEMI or HF. Patients were excluded if they were admitted for the same diagnosis within the last six years, died in the hospital, or left against medical advice. Researchers examined the effect of physician follow-up within one week on the primary outcome of one-month readmission rates. This paper also evaluated the effect of follow-up with the specific physician who treated the patient in the hospital. The rate of early follow-up was 76.6% for patients with NSTEMI and 74.9% for patients with HF. Physician follow-up within one week of discharge was associated with a lower readmission rate compared with late or no follow-up for patients with NSTEMI (n=5,008; hazard ratio [HR] 0.47; 95% CI, 0.39–0.57) and for patients with HF (n=13,577; HR 0.54; 95% CI, 0.48–0.60). Follow-up with the same physician who treated the patient in the hospital was associated with a decreased readmission rate versus follow-up with a different physician for both patients with NSTEMI (HR 0.56; 95% CI, 0.48–0.65) and patients with HF (HR 0.69; 95% CI, 0.62–0.76). This paper did not adjust for disease severity as a confounder for readmission rates. EBP

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The authors declare no conflicts of interest.

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Probiotics for preventing acute otitis media in children

Scott AM, Clark J, Julien B, et al. Probiotics for preventing acute otitis media in children. Cochrane Database Syst Rev. 2019;6(6):CD012941. Published 2019 Jun 18. doi: 10.1002/14651858.CD012941.pub2

DOI 10.1097/EBP.0000000000001595

This systematic review and meta-analysis addressed the benefits of probiotics to prevent or reduce the severity of acute otitis media (AOM) in children. Seventeen randomized controlled trials (RCTs) compared various probiotic formulations with placebo or no treatment (1 study; n=222) and included children up to 18 years old (n=3,488). Mean age was 2.4 years old. Eleven RCTs evaluated *Lactobacillus*-containing probiotics (N=2,507) and six RCTs evaluated *Streptococcus*-containing probiotics (N=981). Duration of follow-up ranged from 20 days to 2 years.

The proportion of children who experienced one or more episodes of AOM during the treatment was lower in those taking probiotics compared with placebo or usual care (16 trials, N=2,961; relative risk [RR] 0.77; 95% CI, 0.63–0.93; number needed to treat [NNT]=10; moderate-certainty evidence). In a subgroup of children who were otitis prone (which was not defined), no difference was noted in the proportion of children with AOM between probiotic and comparator groups (5 trials, N=734; RR 0.97; 95% CI, 0.85–1.1; high-certainty evidence). In the subgroup of children not prone to otitis media, a lower proportion of children receiving probiotics experienced AOM compared with placebo (11 trials, N=2,227; RR 0.64; 95% CI, 0.49–0.84; NNT=9; moderate-certainty evidence). No difference in adverse events was noted between the groups. Children taking probiotics were less likely to take antibiotics for any reason compared with controls (8 trials, N=1,768; RR 0.66; 95% CI, 0.51–0.86; NNT=8; moderate-certainty evidence) and were less likely to have a diagnosis of other infections (11 trials; N=3,610; RR 0.75; 95% CI, 0.65–0.87; NNT=12; moderate-certainty evidence). Limitations of the meta-analysis included significant heterogeneity in probiotics formulations, dosage, timing, and duration of administration among trials. Results were inconsistent among groups with high and low prevalence of previous AOM. No data about cost were provided. Twelve of the 17 trials included in this review were funded by industry.

Methods

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

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

Bottom line: This systematic review and meta-analysis showed inconsistent benefits of probiotics to prevent AOM in children, with no statistically significant improvement in episodes of AOM in children prone to infections—the group who could benefit the most. The significant heterogeneity among probiotic products and concerns for industry conflict of interest also preclude a recommendation to change practice.

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The authors declare no conflicts of interest.

Does it matter the type of IUD used for emergency contraception?

Turok DK, Gero A, Simmons RG, et al. Levonorgestrel vs. copper intrauterine devices for emergency contraception. *N Engl J Med*. 2021;384(4):335-344. doi:10.1056/NEJMoa2022141.

DOI 10.1097/EBP.0000000000001561

This single-blinded noninferiority trial randomized 711 women 18 to 35 years old who presented to one of six family planning clinics in Utah for emergency contraception (EC) to receive either a 52-mg levonorgestrel IUD (LNG-IUD) or a copper T380A IUD (C-IUD). Patients reported unprotected intercourse within the previous

five days, desired to prevent pregnancy for one year, had regular menstrual cycles, knew their last menstrual cycle within three days, were willing to comply with the study protocol, and spoke English or Spanish fluently. The investigators chose a noninferiority margin of 2.5%, the same margin used in studies of oral EC. They assumed unintended pregnancy (UP) rates of 0.1% for the C-IUD and 1% for the LNG-IUD based on previous studies. To achieve 80% power that the 95% CI for the difference between the groups did not cross this 2.5% noninferiority margin, the study required 335 participants in each arm of the study. Ultimately, 356 patients were randomized to the C-IUD arm, of which 321 participants were included in the modified intention-to-treat analysis (MITA), and 355 patients were randomized to the LNG-IUD arm, with 317 participants included in the MITA. Patients not included in the MITA had failed insertion of the device, failed the screening process after being consented, were lost to follow-up (6 in each group), withdrew, discontinued the IUD, or were withdrawn by the investigator. Patients were to perform home pregnancy tests the day before their one-month follow-up, and the pregnancy test was repeated at that follow-up. In addition, patients were surveyed at 1, 3, and 6 months. Only one UP was reported in the LNG-IUD group of 317 participants (0.3%; 95% CI, 0.01 to 1.7), and zero UP was reported in 321 participants in the C-IUD arm (0%; 95% CI, 0 to 1.1). Of the 321 patients in MITA of the C-IUD arm, 300 were determined not to be pregnant at one month based on negative pregnancy tests, and another 21 based solely on clinical and survey data. Of the 317 patients in the MITA of the LNG-IUD arm at one month, 289 had negative pregnancy tests, one had a positive test, and another 27 were determined not to be pregnant based on clinical and survey data. These clinical data were derived by reviewing records at all six family planning clinics. The investigators reported high certainty that if a patient had returned for an abortion, these data would be captured in this system. The number of patients who required clinical data only to determine pregnancy at one month was not reported for either arm. Adverse events resulting in patients seeking medical care within the first month occurred in 5.2% of the LNG-IUD group and 4.9% in the C-IUD group (absolute risk difference was –0.2 (95% CI, –3.6 to 3.3).

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching PubMed with the terms "intrauterine devices", "emergency contraception", and "contraception, postcoital/methods*" to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: This study used 2.5% as the noninferiority margin, as in oral EC noninferiority studies. Although that margin is appropriate for oral ECs based on their failure rates, the expected failure rates for IUDs are much lower (C-IUD=0.1%; LNG-IUD=1%). This would have warranted a lower noninferiority margin. In addition, the study did not meet the required enrollment for the MITA based on the current power analysis, further weakening the authors' assertion of noninferiority.

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Do children benefit from antibiotic treatment of asymptomatic cervical lymphadenopathy?

EVIDENCE-BASED ANSWER

It is unclear. With a two-week course of antibiotics, 80% to 90% of palpable low-risk nodes will resolve by 8 to 10 weeks (SOR: **B**, small prospective cohort study). However, guidelines discourage empiric antibiotics for asymptomatic lymphadenopathy of <2 cm and instead recommend observation for regression and excisional biopsy for persistent lymphadenopathy that is still present after four to six weeks (SOR: **C**, clinical guidelines).

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A 2016 prospective cohort study (n=218) also conducted in Turkey recruited patients between 13 months and 18 years old with acute (<4 weeks) or chronic (>4 weeks) enlarged lymph nodes larger than 1 cm in the cervical, submental, and submandibular region or 5 mm in the suboccipital, preauricular, and postauricular region.[1] The primary outcome was the number of patients diagnosed with a malignancy. All patients underwent initial laboratory evaluation with a blood smear and complete blood count, erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, and uric acid level. Following laboratory evaluation, if there remained a low suspicion for malignancy, patients received antibiotics (amoxicillin, amoxicillin–clavulanate, cefuroxime, or ampicillin–sulbactam) for 14 days. If no decrease in the node size was documented after antibiotic therapy, additional testing included tuberculin skin test, ultrasonography, chest radiography and serology for Epstein–Barr virus (EBV), cytomegalovirus, parvovirus B19, and mycoplasma pneumonia. All patients were followed for a total of eight weeks and then, biopsy was performed in 23 patients based on laboratory results or lack of response to therapy. Testing identified a specific etiology in 70 patients (32%), most commonly infection (59 patients, 27%), while six patients (2.7%) had malignancies. EBV was the most common infectious cause (27%), followed by group A *Streptococci* (10.8%). After eight weeks, palpable lymph nodes had resolved in 92% (n=201) of children.

A 2021 prospective cohort study (n=100) conducted in Turkey enrolled children 2 to 14 years old with asymptomatic cervical lymphadenopathy larger than 1.5 cm in diameter for at least four weeks.[2] Patients underwent ultrasonography to identify characteristics that could reliably predict benign pathology. All children in the study were empirically treated with appropriate antibiotics for two weeks after enrollment. In 80 patients, lymph nodes decreased in size to <1.5 cm within 10 weeks of antibiotic treatment (mean size 2.6 vs 1.2 cm, $P<.001$). Ultrasonography in these children demonstrated regular margins, ovoid shapes, and shrinkage in lymph node size. Of the 20 patients whose lymphadenopathy persisted after antibiotics, five had tuberculosis adenitis, three had Hodgkin lymphoma, and two had acute lymphoblastic leukemia. Their respective ultrasounds demonstrated irregular margins and round shapes. Study limitations included small sample size.

A 2015 clinical practice guideline released by the Italian Society of Preventive and Social Pediatrics, Pediatric Infectious Diseases, and Pediatric Otorhinolaryngology aimed to provide national consensus-based guidelines for the treatment of cervical lymphadenopathy in children.[3] The recommendations were based on the consensus opinion of a panel of experts in general pediatrics, otorhinolaryngology, microbiology, pharmacology, infectious diseases, immunology, and nursing practice. The panel also included a research methodologist and a patient advocate. The material shared with the panel was obtained by a systematic review of 58 articles of interest. For asymptomatic children with cervical lymphadenopathy with a diameter of <2 cm without inflammatory signs (pain, tenderness, redness, heat, or fluctuance), the expert panel recommended against the empiric antibiotic therapy but rather advised close monitoring for regression of lymphadenopathy in 4 to 6 weeks. In the case of asymptomatic cervical lymphadenopathy with a diameter >2 cm, the panel recommended against the empiric antibiotic treatment but rather advised prompt evaluation for malignancy including a preliminary workup with full blood count; C-reactive protein (CRP); lactate dehydrogenase (LDH); liver enzymes; serology tests for EBV, tuberculin skin test (TST), and interferon-gamma release assay (IGRA); and ultrasound scan for concerning features. EBP

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This clinical question was developed as an HDA through a standardized, systematic methodology with details described **here**.

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Is massage effective therapy for tension headaches?

EVIDENCE-BASED ANSWER

For tension headache, myofascial and trigger point release massage may moderately improve perceived headache frequency and headache-related quality of life compared with placebo or usual care (SOR: **C**, small randomized controlled trial [RCT]). Thai massage may be as effective as amitriptyline in reducing pain in chronic tension headache (SOR: **C**, small RCT). A single session of massage therapy may improve headache pain by about 25% compared with placebo (SOR: **C**, small RCT).

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A 2015 randomized controlled trial (RCT; n=56) evaluated the efficacy of myofascial and trigger point release for relieving tension headache in adults.[1] The patients were a mean age of 33.5 years old; 84% were white and 86% were female. The patients reported two or more tension-type headaches per week and those with fibromyalgia, diabetes, depression, neurological or cardiovascular disease, and pregnancy were excluded. Patients taking prophylactic medication or using massage for headache in the previous six months were also excluded. The intervention treatment consisted of 45-minute sessions of myofascial and trigger point release massage applied to various muscle groups in the head, neck, and upper back, administered twice a week for six weeks. Patients in the comparator groups received detuned ultrasound (placebo treatment) or wait-list (pragmatic/usual care). The investigators recorded outcomes at regular intervals starting four weeks before (baseline) and ending four weeks after the intervention (14 weeks total duration). Researchers used data from daily patient diaries to calculate headache frequency, duration, and intensity, and used a 15-point Likert scale, ranging from "a very great deal worse" (–7) to "a very great deal better" (+7), to measure perceived clinical change. They also administered the Headache Disability Inventory (HDI) and Headache Impact Test (HIT-6) to assess changes in quality of life. The HDI measures emotional and functional components of headache and is scored from 0 to 100 ("no" to "severe" disability), where a 16 point or greater decline indicates a clinically meaningful change. The HIT-6 assesses quality of life related to headache frequency, with scores ranging from 36 (minimal impact) to 78 (severe impact), where a decrease of 2.3 to 8 points signifies improvement. Headache frequency, measured at 14 weeks and compared to baseline, was reduced from 3.7 to 2.4 in the massage group (P=.0003) and from 3.8 to 3.0 in the placebo group (P=.013) but was not significantly changed in the wait-list group. No difference was observed in weekly headache frequency reduction between the massage and placebo groups, and none of the groups reported significant changes in headache duration or intensity. For perceived change, 64.3% of patients treated with massage noted a moderate (ie, +4 or +5) or large (ie, +6 or +7) improvement in headache frequency, versus 36.8% for the placebo group and 6.3% for the wait-list group (P=.002). For quality of life, HDI mean scores decreased more over time in the massage group (–8.7 points, P=.0003) than in the placebo (–3.1 points, P=.06) or wait-list (–1.2 points, P=.39) groups. HIT-6 scores improved in both the intervention (–6.1 points, P=.0002) and the placebo (–2.4 points, P=.011) groups but not in the wait-list group (–1.1 points, P=.52).

Another 2015 RCT compared traditional Thai massage to amitriptyline therapy for the treatment of chronic tension-

type headaches (CTTH) in 60 patients recruited from a hospital in Thailand.[2] Patients were on average 49.8 years old and had mean pain scores of 6.2 (out of 10) using the visual analog pain scale (VAS). Patients with moderate nausea, vomiting, prior massage or amitriptyline treatment for CTTH, or other illnesses were excluded. Patients were randomized to treatment with nightly oral amitriptyline 25 mg or twice-weekly 45-minute standardized court-type traditional massage for four weeks. Court-type traditional massage involved applying pressure (usually with the thumbs) to specific points along meridian lines, using "polite gestures" akin to those used in Thai royal courts. Investigators measured VAS scores at two, four, and six weeks. Over the six-week trial period, the VAS pain score improved from 6.3 to 2.6 points in the massage group and from 6.0 to 2.9 in the amitriptyline group. Massage resulted in a greater decrease in mean VAS scores than amitriptyline at all measurement times, with mean differences (favoring massage) between groups of –0.9 (95% CI, –0.54 to –1.3 points) at two weeks, –0.79 (95% CI, –0.42 to –1.5 points) at four weeks, and –0.44 (95% CI, –0.11 to –0.76 points) at six weeks.

A 2009 placebo-controlled, single-blind, crossover RCT in Spain evaluated the immediate effects of head, neck, and shoulder massage on 11 patients with CTTH.[3] Patients had a mean age of 51 years old (88% female). CTTH was diagnosed by a neurologist, with headaches of mild to moderate intensity (≤5 on a 10-point VAS) occurring at least 15 days during the preceding month. Patients were randomly assigned to receive a single 40-minute session of head, neck, and shoulder muscle massage (intervention) or detuned ultrasound applied over the same muscles (control). One week later, the patients crossed over: those treated with massage received detuned ultrasound and those given detuned ultrasound got massage therapy. The outcome assessor was blinded to the treatment received. VAS scores 24 hours after the procedure declined from 4.1 to 3.1 (mean difference [MD] –1.1; 95% CI, –2.0 to –1.0 points) in the intervention group and from 3.7 to 3.6 (MD –0.1; 95% CI, –0.15 to –0 points) in the control group. EBP

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Is medical management comparable with surgical management in adults with uncomplicated appendicitis?

EVIDENCE-BASED ANSWER

Although appendectomy is the definitive treatment of uncomplicated appendicitis, antibiotic-only management results in up to a 70% success at three months and up to 60% success at five years while up to 40% of patients will eventually require an appendectomy. Antibiotic treatment leads to approximately one-third fewer complications and one-half fewer missed days of work. Quality of life and resolution of symptom rates were similar despite the presence of a complicating appendicolith (SOR A: meta-analysis of high-quality randomized controlled trials [RCTs], single RCT, and cohort study).

DOI 10.1097/EBP.0000000000001575

A 2018 systematic review and meta-analysis of seven randomized controlled trials (N=2,017) investigated the efficacy of antibiotic treatment regimens versus surgical treatment of uncomplicated acute appendicitis.[1] The trials included adults (mean age range: 18.5–38

years old) with primarily uncomplicated acute appendicitis. Intravenous antibiotics regimens (24–48 hrs) included a third-generation cephalosporin, metronidazole/tinidazole, beta-lactam, and penicillin. Surgical intervention included open and laparoscopic appendectomy. The primary outcomes included treatment success, length of hospital stay (LOS), overall complications, and recurrence. Follow-up occurred 12 months from initial treatment, with a lost to follow-up rate of 1% to 10%. Antibiotic regimens resulted in lower treatment success compared with appendectomy at one year (71% vs 94%), with no antibiotic regimen superior to the others. The overall complication rate was lower for the antibiotic regimens versus appendectomy (4.4% vs 11.2%). Only treatment with IV piperacillin with tazobactam resulted in a statistically significant 0.6 day (95% CI, –1.1 to –0.15) LOS decrease compared with surgery; however, surgery resulted in a nonsignificant LOS decrease compared with the other antibiotic regimens. The overall appendicitis recurrence rate in the antibiotic group was 18% (5 trials, N=1,725; 95% CI, 8–27.9).

A 2020 US multicenter, nonblinded, noninferiority, randomized trial (n=1,552) compared the quality of life of patients with acute appendicitis receiving either antibiotic or surgical management.[2] The trial included adults (18 years old and older) with acute appendicitis, 414 of whom had an appendicolith. The presence of an appendicolith was considered a complicated appendicitis in previous studies, so a subgroup analysis of these patients was performed. Patients were excluded if they had septic shock, diffuse peritonitis, recurrent appendicitis, evidence of severe phlegmon on imaging, walled-off abscess, free air, evidence of more than minimal free fluid, or suspicion of neoplasm. Patients were randomized to receive either antibiotics (n=776, of whom 212 had an appendicolith) or surgery (n=776, of whom 202 had an appendicolith). Forty-seven percent of patients in the antibiotics group did not require admission but rather completed IV antibiotics in the emergency room and were discharged with a 10-day oral antibiotic regimen. The primary outcome was a 30-day health status assessed with the patient-reported European Quality of Life–5 Dimensions (EQ-5D) questionnaire. The EQ-5D measures mobility, self-care, usual activities, pain, anxiety, and depression (total mean score range: 0–1; higher score indicating higher quality of life). Secondary outcomes included resolution of symptoms (absence of pain, fever, and tenderness), days of missed work within 90 days of treatment, complication rates occurring within 90 days of treatment, and the percentage of patients undergoing appendectomy in the antibiotics group. Mean EQ-5D scores were similar between the antibiotic and appendectomy groups at 30 days (0.92 vs 0.91; 95% CI, –0.001 to –0.03), as well as between those patients with and without an appendicolith (0.92 vs 0.92). Resolution of symptoms was similar for the antibiotic and surgery groups at seven (49% vs 50%; 95% CI, 0.89–1.1), 14 (65% vs 64%, 95% CI, 0.94–1.1), and 30 days (68% vs 70%; 95% CI, 0.91–1.0). Antibiotic treatment resulted in fewer days of missed work compared with surgery (5.26 vs 8.73; 95% CI, 0.51–0.77). Complications were more common in the antibiotics group (8.1 vs 3.5 per 100 patients). Of those receiving antibiotics, 29% had undergone an appendectomy by 90 days (41% of patients with appendicolith versus 25% without appendicolith).

A 2018 5-year observational study (n=257) evaluated the complication rates of patients treated with antibiotics only for CT-confirmed uncomplicated appendicitis.[3] This was a continuation of a randomized controlled noninferiority trial comparing antibiotics management with appendectomy (n=273) over a 1-year period. In the original trial of adults (18–60 years old), 70 patients in the antibiotic group underwent appendectomy within the first year after presentation with appendicitis (27%; 95% CI, 22–33). An additional 30 patients underwent appendectomy from 1 to 5 years with a cumulative incidence of 34% (95% CI, 28–40) at two years, 35% (95% CI, 29–41) at three years, 37% (95% CI, 31–43) at four years, and 39% (95% CI, 33–45) at five years. Of the 100 patients who had an appendectomy in the antibiotics group, seven were found to not have appendicitis on pathology review. The investigators analyzed the five-year overall complication rate (surgical site infections, incisional hernias, abdominal pain, and obstructive symptoms) between patients who were randomized to the appendectomy group versus those in the antibiotics group (not including the 27 patients in the appendectomy and 11 patients in the antibiotic group lost to follow-up). The 5-year complication rate in the appendectomy group was 24% (95% CI, 19–30) and 6.5% (95% CI, 3.8–10) in the antibiotic group ($P<.001$). LOS did not differ between groups, but the number of sick days was greater in the appendectomy group (22 days; 95% CI, 19–23) than the antibiotics group (11 days; 95% CI, 11–12; $P<.001$ between groups). A key limitation was that most appendectomies were performed using an open technique (rather than a laparoscopic approach), likely affecting recovery time and complication rate. EBP

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Does alcohol increase the risk of melanoma?

EVIDENCE-BASED ANSWER

Yes. Heavy alcohol consumption (more than 50 g daily) is associated with an increased risk of melanoma compared with light alcohol consumption (<12.5 g daily), and the increase in risk is linear in increments of 10 g daily (SOR: **B**, meta-analysis of prospective cohort and case-control studies). Alcohol consumption is associated with increased melanoma for moderate drinking (12.5–50 g daily), but not light drinking (<12.5 daily) compared with nondrinkers and occasional drinkers (SOR: **B**, meta-analysis of cohort studies and case-control studies).

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A 2018 systematic review and meta-analysis of six prospective cohort studies, 12 case-control studies, and two pooled case-control studies (N=10,555 melanoma cases and more than 1.6 million noncases/controls) analyzed the association between alcohol intake and melanoma risk.[1] All cases of melanoma were all confirmed with a skin biopsy. Sex and age were adjusted for in all studies, while 11 studies adjusted for skin phenotype and nine for exposure to sunlight. Daily intake levels were converted to any one drink representing 12 g of alcohol consumption. High alcohol consumption was defined as >50 g daily with the lowest alcohol consumption as <12.5 g daily. After pooling 18 studies (N=10,143 cases; 1,559,312 controls), melanoma risk was significantly higher in those in the high alcohol consumption group compared with the low consumption group (summary relative risk [SRR] 1.3; 95% CI, 1.1–1.5). Fifteen studies (N=9,313 cases; 1,489,227 controls) were pooled, and a significant dose-response relationship per 10 g per day consumption was observed in relation to melanoma risk (SRR 1.1; 95% CI, 1.03–1.1). No significant differences were noted between types of alcohol consumption (wine, beer, and liquor).

A 2014 multicenter meta-analysis of 409 case-control studies and 163 cohort studies of 23 site-specific cancer risks (N=486,538 cancer cases) analyzed the effect of alcohol consumption on different types of cancer.[2] A subanalysis of two cohort and 12 case-control studies (N=6,096) specifically examining melanoma and alcohol consumption was performed. Patients consumed all different types of alcohol (beer, wine, and liquor) and were compared with both nondrinkers and occasional drinkers. Alcohol consumption was categorized as light (<12.5 g/d), moderate (12.5–50 g/d), or heavy (>50 g/d). After pooling of the 14 studies, alcohol consumption was associated with an increased risk of melanoma in a dose-risk manner for moderate drinkers (relative risk [RR] 1.2; 95% CI, 1.03–1.4), but not in light drinkers (RR 1.1; 95% CI, 0.97–1.3) as compared with nondrinkers and occasional drinkers. Owing to pooling issues, heavy drinkers were not analyzed. EBP

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In adolescents who receive the first dose HPV vaccination between ages 9 and 14 years old, is a two-dose series as effective as a three-dose series?

EVIDENCE-BASED ANSWER

The two-dose human papilloma virus vaccination series is noninferior to a three-dose series in antibody geometric mean titers and seropositivity for girls 9 to 15 years old. (SOR: **A**, based on systematic review of randomized controlled trials). No difference was noted in genital warts after 4.6 years or cervical intraepithelial neoplasia two or three and adenocarcinoma-in-situ after seven years of follow-up for girls who received a two-dose compared with a three-dose series (SOR: **B**, based on 2 quality diagnostic prospective cohort studies).

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A 2019 systematic review and meta-analysis of four randomized controlled trials (RCTs) compared immunogenicity of a two-dose or a three-dose human papilloma virus (HPV) vaccine in pediatric female patients 9 to 15 years old (N=4,073) recruited from multiple international sites.[1] HPV vaccines included the bivalent, quadrivalent, and nonavalent versions. Three trials included female patients and one trial included female and male patients. Patients received the two-dose series administered at months zero and two, zero and six, or zero and 12 in comparison with the three-dose series administered at months zero, two, and six or zero, one, and six. Outcomes included antibody geometric mean titers (GMTs), a measurement of the antibody produced against a desired antigen, and seroconversion. Seroconversion one month after the final dose showed no difference for all nine HPV subtypes. At 36 months, noninferior GMTs were noted for all genotypes with two doses of the nonavalent vaccine compared with three doses, except HPV45 and HPV52, where noninferiority was inconclusive (1 RCT; n=476-511, depending on HPV subtype). At 60 months, two doses of the bivalent vaccine (1 RCT; n=93) had inconclusive noninferiority for GMTs of HPV16 and HPV18 compared with three doses. At 60 months, two doses of the quadrivalent vaccine (n=101) were noninferior for GMT for HPV6, HPV11, and HPV16, whereas HPV18 results were inconclusive. No studies reported clinical outcomes such as cervical intraepithelial neoplasia (CIN), adenocarcinoma-in-situ, or cervical cancer. The single study that included male patients did not compare the two-dose series with a three-dose series in the male population. No difference in serious adverse events or mortality was noted between two-dose or three-dose regimens up to 60 months.

A 2017 prospective cohort study of adolescent females (9–18 years old, n=387,906) looked at the incidence rates of genital warts in patients who received zero to three doses of the quadrivalent HPV vaccine.[2] In a subset analysis of patients who received their first vaccine before age 15 years old (n=33,851), no significant difference was noted in the development of genital warts at 4.6 years of follow-up in two-dose compared with three-dose recipients (0.51% vs 0.44%, incidence rate ratio 0.91; 95% CI, 0.53–1.58).

A 2014 prospective cohort analysis of female pediatric patients 9 to 18 years old in Australia (n=250,648) assessed the effectiveness of the quadrivalent HPV vaccine by number of administered doses (0–3) against CIN 2 or 3 and adenocarcinoma-in-situ up to seven years after vaccination.[3] Approximately 60% of the patients who received at least one dose (n=201,803) started the series at 14 to 15 years old. Compared with unvaccinated women, the adjusted hazard ratio for combined risk of CIN 2 or 3 and adenocarcinoma-in-situ was significantly lower in the one-dose series (adjusted hazard ratio [aHR] 0.65; 95% CI, 0.52–0.81), two-dose series (aHR 0.61; 95% CI, 0.52–0.72), and three-dose series (aHR 0.59; 95% CI, 0.54–0.65). The adjusted hazard ratio for two-dose recipients was comparable with three-dose recipients for the studied high-grade cervical lesions (aHR 1.00; 95% CI, 0.85–1.17). EBP

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Does prophylactic tranexamic acid reduce postpartum hemorrhage in vaginal deliveries?

EVIDENCE-BASED ANSWER

Prophylactic tranexamic acid (TXA) may decrease the incidence of postpartum hemorrhage (PPH) of >500 mL in vaginal deliveries but does not seem to decrease severe PPH of >1000 mL (SOR: B, meta-analysis of RCTs). Prophylactic TXA may decrease provider assessment of clinically significant PPH and the use of additional uterotonic agents and does not decrease more patient-oriented outcomes of PPH such as the need for blood transfusion, arterial embolization, or surgery (SOR: B, RCT).

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A 2019 meta-analysis of four RCTs examined the effectiveness of tranexamic acid (TXA) given prophylactically within 10 minutes after vaginal delivery in 4,671 immediate postpartum patients.[1] All four RCTs recruited nulliparous women with a vertex presentation. Three of the four studies included only singleton pregnancies at term with anticipated spontaneous vaginal delivery, whereas one study included singleton and twin gestations and estimated gestational ages >34 weeks. Two of the four RCTs explicitly excluded pregnancies complicated by polyhydramnios, fetal macrosomia, preeclampsia, and previous history of postpartum hemorrhage (PPH). In all studies, patients were given either 1 g TXA IV or placebo immediately postpartum, both in addition to standard of care oxytocin, cord traction, and fundal massage. Researcher assessed for the primary outcome of postpartum hemorrhage and secondary outcomes of mean blood loss, severe postpartum hemorrhage, transfusion needs, and thromboembolic events. Compared with placebo, women who received prophylactic TXA had a lower incidence of primary postpartum hemorrhage, defined as 500-mL blood loss within 24 hours after delivery (8.7% vs 11.4%, risk ratio [RR] 0.61; 95% CI, 0.41–0.91) and lower mean blood loss (3 trials; N=832; mean difference –85 mL; 95% CI, –110 to –60). Researchers did not find a significant difference in severe postpartum hemorrhage, defined as 1,000 mL or more of blood loss (3 trials; N=4,363; RR 0.57; 95% CI, 0.27–1.2) or in other clinically important secondary outcomes related to PPH such as use of additional uterotonic medications (3 trials; N=4,363; RR 0.55; 95% CI, 0.3–1.0) or blood transfusion (2 trials; N=4,243; RR 0.87; 95% CI, 0.46–1.6). Regarding adverse effects of TXA, they found no significant difference in thrombotic events between groups (4 trials; N=4,636; RR 0.25; 95% CI, 0.03–2.2) but did find an increased risk of nausea (3 trials; N=4,363; RR 2.3; CI, 1.8–3.0) and vomiting (2 trials; N=4,243; RR 2.2; 95% CI, 1.7–2.8) in the TXA group.

The largest of the four trials included in the above meta-analysis, discussed here for additional outcomes of provider-assessed clinically significant PPH and longest duration of follow-up of the included studies, was a 2018 multicenter, double-blind RCT, in which 4,079 immediate postpartum women were randomized to receive either TXA or placebo in addition to oxytocin after vaginal delivery.[2] Women 18 years old and older with a singleton pregnancy at estimated gestational age of 35 weeks or more and planning to have a vaginal delivery were recruited. The study excluded women with increased risk of venous or arterial thrombosis or bleeding, conditions impairing hemostasis, epilepsy or seizures, or poor language comprehension. This study found no

significant difference in the primary outcome of postpartum hemorrhage (defined as 500-mL blood loss within 24 hours after delivery) (RR 0.83, 95% CI, 0.68–1.01). However, it did find a significant decrease in provider-assessed clinically significant PPH (RR 0.74; 95% CI, 0.61–0.91) and use of additional uterotonic medications (RR 0.74; 95% CI, 0.61–0.91). Provider-assessed clinically significant PPH was determined by the blinded delivering providers' response to the question, "Was there a PPH?" once the patient was discharged from the labor ward. Researchers found no differences in other secondary outcomes between groups including other measures of PPH severity and impact such as blood loss, blood transfusion, arterial embolization, or surgery for PPH, as well as no difference in the rate of thrombotic events after three months of delivery, which is the longest follow-up of any of the studies included in the previous meta-analysis. EBP

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Does fish oil supplementation improve patient-oriented cardiovascular outcomes in adults with hyperlipidemia?

EVIDENCE-BASED ANSWER

Daily eicosapentaenoic acid (EPA) plus docosahexaenoic acid is not effective for primary cardiovascular protection in hyperlipidemic adults on statin therapy (SOR: **B**, large randomized controlled trial [RCT]). Daily EPA does seem effective for secondary prevention of cardiovascular events in younger men (SOR: **A**, consistent evidence from 2 large RCTs). Fish oil may increase fibrillation risk (SOR: **C**, mixed evidence from 3 RCTs).

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A 2020 double-blind randomized controlled trial (RCT; n=13,078) assessed the incidence of cardiovascular events with EPA plus docosahexaenoic acid (DHA) supplementation in hyperlipidemic adults over a median of 3.2 years.[1] Patients were majority male, had a mean age of 63 years old, and were recruited from over 600 hospitals in 22 countries. Patients were on statin therapy for at least four weeks because of dyslipidemia (triglycerides 180–499 mg/dL, HDL <42 mg/dL for men and <47 mg/dL for women, LDL <100 mg/dL) and high cardiovascular risk based on established atherosclerotic disease or equivalent risk via other risk factors. Patients with an ischemic event within the past 30 days, baseline use of fibrates, on weight loss medications, or on omega-3 supplements were excluded. Patients were randomized equally to oral EPA plus DHA 4 g daily or placebo corn oil pills. The primary composite outcome was cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization. No difference in risk was noted between the EPA/DHA group and the placebo group for the composite outcome (hazard ratio [HR] 0.99; 95% CI, 0.90–1.1), causing the study to be terminated early. The EPA/DHA group did have a significant increase in new-onset atrial fibrillation (HR 1.7; 95% CI, 1.3–2.2). However, the EPA/DHA group did have a significant reduction in coronary events in patients with established cardiovascular disease (HR 0.85; 95% CI, 0.75–0.97). The EPA/DHA had a higher incidence of gastrointestinal side effects (25% vs 15%, no *P* value) but not bleeding events.

A 2019 double-blind RCT (n=8,179) examined the occurrence of cardiovascular events with EPA supplementation in hypertrigyceridemic adults.[2] Patients

were majority male, a mean age of 64 years old, recruited from 11 difference countries, and were followed for a median of 4.9 years. Patients were on statin therapy for at least four weeks with isolated hypertriglyceridemia (triglycerides 135–499 mg/dL with LDL 41–100 mg/dL) and were either 45 years or older with established cardiovascular disease or 50 years or older with diabetes and one cardiovascular risk factor. Patients with severe heart failure, liver disease, hyperglycemia, planned coronary procedure, or history of pancreatitis were excluded. Participants were equally randomized to oral EPA 2 g twice daily or placebo mineral oil pills. The primary outcome was a composite outcome of any occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. Secondary outcomes included emergency or urgent revascularization, cardiovascular death, hospitalization for unstable angina, stroke, all-cause mortality, and the primary composite outcome without revascularization and unstable angina. Compared with the mineral oil group, the EPA group had a significantly lower risk of the primary composite outcome (HR 0.75; 95% CI, 0.68–0.83), the secondary composite endpoint (HR 0.74; 95% CI, 0.65–0.83), and all other secondary endpoints except all-cause mortality. Subgroup analyses revealed no benefit for primary prevention or for certain patients (65 years or older, female, and baseline triglycerides <150 ng/dL). The EPA group had a significant increase in atrial fibrillation (5.3% vs 3.9%, $P<.05$) and peripheral edema (6.5% vs 5.0%, $P<.05$).

A 2007 open-label RCT (n=18,645) measured incidence of various cardiovascular events with EPA supplementation in hyperlipidemic adults from physician offices in Japan with five-year follow-up.[3] Patients were <75 years old with hyperlipidemia (total cholesterol ≥250 mg/dL and LDL ≥170 mg/dL) on statin therapy with or without coronary disease. Patients with cardiovascular events within the past six months or existing significant comorbidities were excluded. Patients were randomized to oral EPA 1,800 mg daily or no intervention. The primary outcome was a composite outcome of cardiac death, myocardial infarction, unstable angina, angioplasty, stenting, or coronary artery bypass. Secondary outcomes were all-cause mortality, and cardiovascular mortality and morbidity. Compared with the placebo group, the EPA group had lower risk of the composite outcome (HR 0.81; 95% CI, 0.69–0.95), unstable angina (HR 0.76; 95% CI, 0.62–0.95), and nonfatal coronary events (HR 0.81; 95% CI, 0.68–0.96) compared with the no intervention group. No difference was noted between groups for incidence of sudden cardiac death (HR 1.1; 95% CI, 0.55–2.1) or hemorrhagic stroke (HR 1.1; 95% CI, 0.91–1.4). Subgroup analyses demonstrated no benefit for primary prevention and for certain patient groups (>60 years, female, smokers, diabetic, or normotensive). Compared with the placebo group, the EPA group had more adverse events (25% vs 22%, $P<.0001$), including joint or muscle pain, gastrointestinal disturbance, rash, hemorrhage, and transaminitis. EBP

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In adults, does apple cider vinegar consumption increase intentional weight loss?

EVIDENCE-BASED ANSWER

Perhaps. Apple cider vinegar (ACV) consumption may increase weight loss, although to an uncertain degree of clinical significance (SOR: **B**, systematic review of randomized controlled trials [RCTs] with low quality). Adding 30 mL ACV daily to a restricted calorie diet may increase weight loss by an additional 1.7 kg over the course of 12 weeks (SOR: **C**, small RCT).

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A 2020 systematic review of 25 studies (N=493), consisting of 10 randomized controlled trials (RCTs), three non-RCTs, and 12 animal studies, evaluated the safety and efficacy of apple cider vinegar (ACV) to improve various biophysical and metabolic parameters.[1] Only three RCTs (N=216) reported body weight. For these RCTs, patients were 56% male with a mean weight of 75 kg and between 20 and 80 years old. Patients' health conditions varied greatly across the three trials, ranging from healthy to those diagnosed with prediabetes or type-2 diabetes. Intervention groups ingested various ACV dosages ranging from 15 to 120 mL per day while controls included several forms of placebo and mimicry such as 30–80 mg acetic acid pills or 1,250 mg lactic acid. The outcomes were weight and body mass index (BMI) over 12 weeks.

Significant reductions in body weight (1 RCT, n=175; mean difference [MD] –1.5 kg; $P<.001$) and BMI (1 RCT, n=175; MD –0.5 kg/m^2; $P<.001$) were reported between daily 30 mL ACV consumption and placebo (1,250 mg lactic acid mimic); furthermore, when compared with 15 mL daily ACV (700 mg acetic acid), the higher 30 mL dose (1,500 mg acetic acid) showed a modest, relatively greater reduction of weight (1 RCT, n=175; MD –0.7 kg; $P<.01$) and BMI (1 RCT, n=175; MD –0.3 kg/m^2; $P<.01$). By contrast, no significant change was observed in weight and BMI (1 RCT, n=14; MD not reported) between 15 mL twice daily ACV use and control (1 ACV pill twice daily, 80 mg acetic acid). In addition, no significant change in weight loss (1 RCT, n=27) was noted between high-dose 60 mL twice daily ACV (2,800 mg acetic acid) and placebo (1 pill twice daily, 30 mg acetic acid). No adverse effects were reported. This study was limited by heterogeneity of study designs, lack of meta-analysis, limited and inconsistent reporting of weight data across studies, and unclear and high risk of bias.

A 2018 two-arm parallel RCT (n=44) examined the impact of ACV consumption on weight loss and various serum and anthropometric measures for patients undergoing restricted calorie dieting.[2] Metabolically healthy patients were enrolled from a nutrition clinic in Iran and were predominantly 82% female with a mean age of 43 years old, mean weight of 83 kg, and a mean BMI of 32 kg/m^2. Patients with ACV ingestion within one month, with infectious or gastrointestinal disease, thyroid dysfunction, or diabetes were excluded. The intervention group (30 mL daily ACV consumption with a 250 kcal/d deficit restricted calorie diet) and the control group (diet alone) were compared at baseline, six, and 12 weeks. ACV with dieting significantly reduced body weight (MD –1.7 kg, $P<.05$) and BMI (MD –0.63 kg/m^2, $P<.05$) compared with diet alone. This study was limited by lack of blinding. EBP

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In nonsmoking pregnant patients, is maternal caffeine consumption associated with low birth weight?

EVIDENCE-BASED ANSWER

Yes. Increased maternal caffeine consumption as little as 50 mg/d is associated with lower birth weight. This finding remains consistent between serum caffeine concentrations and self-reported caffeine consumption (SOR: **B**, large meta-analysis of observational studies and prospective cohort study). However, an association is not proof of causation, and other factors may influence the association.

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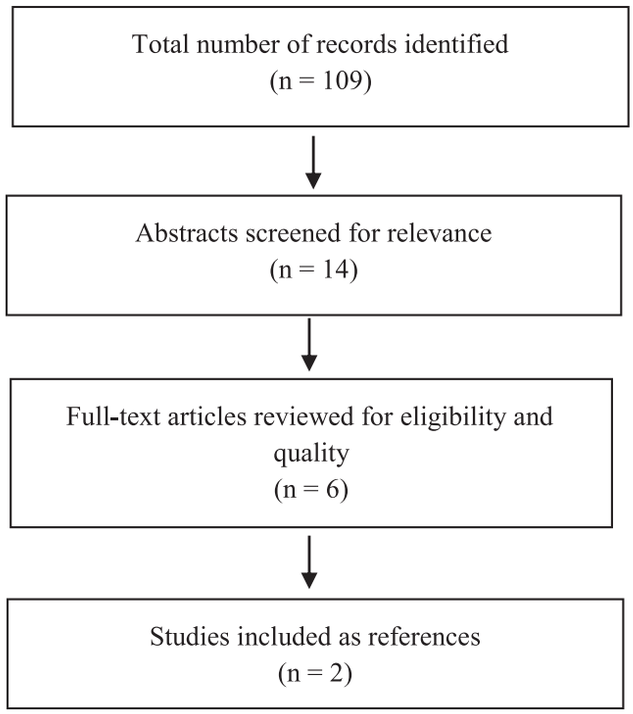

FIGURE 1. Literature search flow diagram

Methods

The authors developed the clinical question, "In nonsmoking pregnant patients is maternal caffeine consumption associated with low birth weight?" based on the clinical needs of their practice site. EBP editors approved the question based on its relevance and applicability to practicing primary care clinicians. EBP editors also verified that the question does not duplicate other HelpDesk Answers written in the prior three years.

The table includes the databases and search terms the authors used to find studies matching the following study inclusion criteria: patients—nonsmoking pregnant female patients; intervention—maternal caffeine consumption; comparison—no caffeine consumption to very low caffeine consumption; and outcome—fetal growth restriction. Authors selected the most relevant, highest evidence–level studies published within the last eight years to prepare the HDA manuscript (see **TABLE 1**; see **FIGURE 1**).

Evidence summary

A 2014 systematic review and meta-analysis of 13 prospective cohort or nested case-control studies (N=100,762) examined the dose-response association of maternal caffeine intake during pregnancy, birth weight, and related outcomes such as small for gestational age and intrauterine growth restriction.[1] Studies needed to have reported risk of low birth weight with associated maternal caffeine intake and consider potential confounding factors such as maternal smoking and diabetes. In a subset of 11 studies reporting birth weight as a binary variable (N=90,747), an association of all levels of caffeine intake was observed compared with <50 mg/d (relative risk [RR] 1.1; 95% CI, 1.1–1.2 for 50–149 mg/d; RR 1.4; 95% CI, 1.2–1.6 for 150–249 mg/d; and RR 1.6; 95% CI, 1.2–2.1 for >350 mg/d). In a subset of 4 studies reporting birth weight as a continuous variable (N=10,015), no significant difference was observed in birth weight for caffeine intake of 50 to 149 mg/d compared with <50 mg/d, but higher levels of caffeine intake were associated with lower birth weight (–33 g, 95% CI, –4 to –63 g for 150–249 mg/d and –69 g, 95% CI, –35 to –102 g for >350 mg/d). Dose-response meta-analysis results showed a 13% higher risk of low birth weight for each 100 mg/d increment of maternal caffeine intake. The limitations of this review included self-

TABLE 1. HDA search strategy

Search engine	Search term or combination of search terms	Total no. of records identified
PubMed Clinical Queries	a) Fetal growth restriction and maternal caffeine consumption	20
Trip Database	a) Fetal growth restriction and maternal caffeine consumption b) Low birth weight and maternal caffeine consumption	86 77
Cochrane Library	a) Fetal growth restriction and maternal caffeine consumption	1
ECRI Guidelines Trust	a) Fetal growth restriction and maternal caffeine consumption	2

reported caffeine consumption, unclear influence of birth weight by duration of gestation, and the potential for residual confounding in observational studies.

A 2021 prospective cohort study (n=2,055) assessed the relationship between first trimester maternal caffeine consumption in nonsmoking pregnant patients and neonatal anthropometric data.[2] Patients had low-risk pregnancies between 8 and 13 weeks' gestation, body mass index 19.0 to 29.9 kg/m^2, and no history of prepregnancy chronic conditions. The mean age was 28 years old, and the patient population was quite demographically heterogenous with 28% Hispanic and 19% Asian and Pacific Islander identification. Investigators interviewed patients about daily caffeine consumption and assessed serum caffeine and paraxanthine (the primary metabolite of caffeine). Fetal growth ultrasounds occurred across six prenatal visits while neonatal anthropometric data were assessed within 1 to 3 days after birth. The first quartile serum caffeine concentration was <28 ng/mL while fourth quartile serum caffeine concentration was >658.8 ng/mL. Patients in the highest quartile for caffeine concentration had infants with lower birth weight compared with the lowest quartile (difference of –84 g; 95% CI, –146 to –23). Analysis of birthweight as a continuous variable demonstrated that each standard deviation increase in log serum caffeine concentrations correlated with a decrease in birth weight (–26 g; 95% CI, –47 to –5; *P*=.004). Patients who self-reported caffeine consumption more than 50 mg/d also had lower average birth weights compared with patients reporting no caffeine consumption (–66 g; 95% CI, –121 to –10). Limitations of this study included patients with fourth quartile caffeine intake being statistically older and more likely to be non-Hispanic White, parous, and married than those with first quartile intake. EBP

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In adults with nonspecific acute or chronic low back pain, do NSAIDs offer pain reduction over placebo?

EVIDENCE-BASED ANSWER

Nonsteroidal anti-inflammatory drugs (NSAIDs) are slightly better at reducing pain than placebo for patients suffering from acute or chronic low back pain, but the pain reduction may not be clinically relevant (SOR: **A**, 2 systematic reviews of randomized controlled trials).

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A 2020 systematic review of 32 randomized controlled trials (RCTs; N=5,356) examined the effects of NSAIDs on acute low back pain (LBP) compared with placebo.[1] Four RCTs (N=815) were identified for a subanalysis of pain reduction. Acute LBP was defined as pain below the costal margin and above the gluteal folds lasting <12 weeks. Those with chronic LBP, flare-ups, or sciatica were excluded. Adults, in primary or secondary care settings, received diclofenac 25 to 75 mg daily or 50 mg twice daily (2 trials), piroxicam 40 mg daily for two days followed by 20 mg daily (1 trial), or ibuprofen 400 to 1,200 mg daily (1 trial). Pain levels were measured using a 0 to 100 visual analog scale (VAS) with lower scores indicating reductions of pain and with follow-up ranging from 1 to 12 weeks. After pooling of all four trials, NSAIDs significantly reduced pain intensity more than placebo (mean difference [MD] –7.3; 95% CI, –11 to –3.6). The magnitude of the decrease in pain intensity was small and possibly was not clinically relevant. No minimum clinically important difference (MCID) was defined. Based on the available literature, the MCID for acute pain has been considered anywhere from eight and up on a 100-point scale. Key limitations include lack of randomization procedure information, allocation concealment, and selective reporting bias.

A 2016 systematic review of 13 RCTs (N=4,807) analyzed the effects of NSAIDs on chronic LBP compared with placebo.[2] Again, six RCTs (N=1,354) were identified for a subanalysis of pain reduction. Chronic LBP was defined as pain lasting for at least 12 weeks. Patients with sciatica or a known etiology of chronic LBP (e.g., infection, neoplasm, metastasis, osteoporosis, rheumatoid arthritis, or fractures) were excluded. Adults, in general practice and outpatient clinics, received various oral NSAIDs, with the most common being naproxen 1,000 mg daily for 16 weeks (3 trials). Patients reported pain levels from baseline using a similar 0 to 100 VAS (as reported above) at a median follow-up of eight weeks. After pooling of all six trials, NSAIDs significantly reduced pain intensity more than placebo (MD –7.0; 95% CI, –10 to –3.2). The decrease in pain intensity was small, and again, no MCID was provided for chronic pain. Based on the available literature, the median absolute MCID for chronic pain is considered 23 on a 100-point scale. Key limitations include high dropout rates and relatively short follow-up times. EBP

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Is buprenorphine safe for the treatment of chronic pain in adults?

EVIDENCE-BASED ANSWER

Yes. Buprenorphine in various forms (ie, intravenous, transdermal, sublingual, and buccal) controls chronic pain without severe adverse reactions (SOR: **A**, systematic review of randomized controlled trials). Transdermal buprenorphine reduces pain; however, mild-to-moderate side effects may limit its tolerability in some patients (SOR: **C**, single open-label study). Buprenorphine should be considered over Schedule II opioids for chronic pain because of its effectiveness and lower risk of severe side effects (SOR: **C**, expert opinion).

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A 2017 systematic review compiled data from 25 randomized control trials of patients 18 years old and older with pain lasting at least three months (N=1,668).[1] Included studies assessed the effectiveness and tolerability of five different formulations of buprenorphine: transdermal delivery system (TDS) buprenorphine, buccal buprenorphine, sublingual buprenorphine, sublingual buprenorphine/naloxone, and IV buprenorphine. The intervention was buprenorphine at any dose or route. The controls were placebo or opioid analgesics (morphine, oxycodone, TDS fentanyl, tramadol, or methadone). The types of chronic pain were low back pain, osteoarthritis, neuropathy, and cancer-related pain. Efficacy was the primary outcome, measured by a reduction of pain on either a Likert scale or an 11-point visual or numeric rating scale ranging from 0 (no pain) to 10 (severe pain). The secondary outcome was adverse effects. Fourteen of the 25 studies demonstrated clinically significant improvement in pain with buprenorphine. Of those, 11 compared buprenorphine with placebo and three compared buprenorphine with another opioid. A TDS was used in most studies and was the most efficacious, with 10 of the studies being positive against placebo. This was demonstrated by clinically significant pain relief, defined either as a lower overall pain score or as a mean reduction in the pain score compared with the control (statistics not provided). The most common adverse effects seen with TDS buprenorphine were gastrointestinal complaints (21%), neurologic symptoms (14%), and administration site issues (17%). In the double-blind phase of one trial of TDS buprenorphine, the incidence of adverse events in the placebo group matched that in the treatment group (52% vs 55%). The most common adverse effect seen in trials of buccal buprenorphine was nausea in opioid-naive patients. No severe adverse effects were reported in any studies. The limitations of this review included a considerable variation in doses and formulations of buprenorphine, use of multiple pain scales, and types of chronic pain evaluated.

A 2017 prospective, open-label, single-arm study in Hong Kong, Korea, and the Philippines evaluated the effectiveness and tolerability of transdermal buprenorphine in the treatment of chronic pain (n=114).[2] Patients included in the study were 18 to 80 years old without a history of opioid use and with chronic pain that was not controlled by nonopioids, defined as a score ≥ 4 on the Box Scale-11 (BS-11) pain scale that ranged from 0 (no pain) to 10 (worst imaginable pain). Types of chronic pain included in the study were low back, joint/muscle, rheumatoid arthritis, and osteoarthritis. Patients with cancer, pregnancy, history of substance abuse, or of child-bearing age and not on appropriate contraception were excluded. Seventy-six percent of patients were female, and the most common types of pain were osteoarthritis and low back pain. Over six weeks, participants were started on 5 μg of a seven-day TDB patch and titrated up to a maximum of 40 μg to achieve optimal pain control. Those who reached optimal control began an 11-week treatment period. At each visit, patients rated their BS-11 pain score. The mean baseline score was 6.2, and the estimate of least squares mean change in scores was –2.6 (95% CI, –3.1 to –2.2). Of the 114 participants, 50 did not complete the study, and 33 of those patients dropped out because of adverse events. Sixty-eight percent of patients had adverse outcomes attributed to TDB, the most common of which were nausea (39.5%), constipation (31.6%), dizziness (27.2%), somnolence (19.3%), vomiting (16.7%), headache (8.8%), pruritus (7.9%), and application site reactions (6.1%). Far fewer adverse events were reported in Korea, where prophylactic antiemetics and laxatives were prescribed more frequently per guideline recommendations. No significant changes were noted in

vitals or physical examination findings or any unexpected safety concerns. This study was limited in that it only included Asian patients, most of whom were female, limiting its application to a broader population. In addition, the short 11-week course cannot be used to assess the efficacy and safety of long-term TDB therapy.

A 2020 panel of experts from The American Academy of Pain Medicine manually selected articles on the appropriate use of buprenorphine for chronic pain after a literature search did not yield any results.[3] These studies were discussed at a consensus conference that followed standards set by the National Institutes of Health Methodology. The panel recommended that buprenorphine (Schedule III) be considered over Schedule II opioids such as fentanyl and oxycodone in managing chronic pain because of its reduced barriers to access, slower onset of tolerance, and reduced risk of respiratory depression in the absence of concomitant nonopioid sedative and anticonvulsant use. The panel noted that buprenorphine could reach therapeutic levels while maintaining a relative ceiling effect for respiratory depression. In addition, the panel recommended that buprenorphine be considered over opioids such as tramadol or codeine in patients who are known rapid CYP2D6 metabolizers. The authors did not provide a level of evidence for their consensus statements. EBP

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This clinical question was developed as an HDA through a standardized, systematic methodology with details described **here**.

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In patients with dementia, which pharmaceutical interventions are effective at reducing agitated behaviors?

EVIDENCE-BASED ANSWER

Aripiprazole mildly decreases symptoms of agitation in patients with dementia and has a low side effect profile (SOR: **A**, network meta-analysis of randomized controlled trials [RCTs]). Initiation of antidepressants with serotonergic activity is mildly effective at decreasing symptoms of agitation in patients with dementia with minimal side effects (SOR: **A**, meta-analysis of RCTs). Valproate preparations do not decrease symptoms of agitation in patients with dementia (SOR: **A**, systematic review). The atypical antipsychotic brexipiprazole does not decrease agitation symptoms in patients with Alzheimer's dementia (SOR: **B**, 2 RCTs).

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A 2019 network meta-analysis of 17 randomized controlled trials [RCTs] with a total of 5,373 patients analyzed the effectiveness of atypical antipsychotics versus placebo in improving agitation in dementia.[1] The studies followed outcomes over a period of 6 to 32 weeks. Patients were 65 years old or older and had a clinical diagnosis of dementia. Twelve of the studies were conducted solely in nursing homes, three in the outpatient setting, and two included participants from both settings. Treatment medications included quetiapine, risperidone, olanzapine, and aripiprazole.

Aripiprazole demonstrated a small improvement in agitation as measured by the Cohen-Mansfield Agitation Inventory (CMAI) with a standard mean difference (SMD) of –0.30 (95% CI, –0.35 to –0.05). Risperidone similarly demonstrated a small decrease in agitation with an SMD of –0.26 (95% CI, –0.37 to –0.15). Quetiapine and olanzapine did not relieve agitation symptoms by the CMAI scale. Safety analyses showed risperidone and olanzapine increased rates of cerebrovascular adverse events, and all the medications were associated with sedation. Limitations of this network analysis included limited data sets for quetiapine and olanzapine (Methods, Supplemental Digital Content 1, http://links.lww.com/FPIN/A10).

A meta-analysis from 2021 of 14 RCTs (N=1,357) compared the mean change in scores of neuropsychiatric symptoms and agitation using validated scales between serotonergic antidepressant medications and placebo.[2] Patients were diagnosed with Alzheimer's disease, vascular dementia, or frontotemporal dementia. The mean patient age was 76.8 years old with 733 in the treatment group and 614 in the placebo group. Treatment medications included multiple serotonergic antidepressants such as sertraline, fluoxetine, mirtazapine, and citalopram. Initiation of serotonergic medications to treat agitation led to a significant, although small decrease in symptoms of agitation (effect size = –0.28; 95% CI, –0.43 to –0.14, $P<.001$). Nine of the 14 RCTs provided data on adverse events, and no difference was observed in the number of events between placebo and treatment groups. Limitations of the study included most patients being diagnosed with Alzheimer's dementia, the broad inclusion of antidepressants with serotonergic activity without respect to their primary mechanism of action, and variable dosing regimens.

The use of valproate for management of agitation in patients with dementia was assessed in a 2018 meta-analysis of five RCTs (N=430).[3] Patients were required to either have been diagnosed with dementia by the *Diagnostic and Statistical Manual of Mental Disorders-5* or have other evidence of dementia on medical or psychological examination. All patients were institutionalized either in long-term care or in psychiatric hospitals. The intervention was a minimum of one week of treatment with valproate preparations versus placebo. Agitation posttreatment was measured using either CMAI or another validated scale. No improvement in symptoms of agitation was noted in any of the included studies. Major adverse events encountered included hyponatremia, thrombocytopenia, and oversedation. One of the included studies had a high level of attrition because of adverse events (22% of treatment group).

A 2021 study included two RCTs (N=703) that assessed changes in the CMAI score in patients with Alzheimer's dementia 12 weeks after initiation of brexpiprazole 0.5 to 2 mg, an atypical antipsychotic.[4] Patients had a diagnosis of Alzheimer's disease and were 55 to 90 years old. Patients were required to have symptoms of baseline agitation, defined by a score of 4 or greater on the Neuropsychiatric Inventory-Nursing Home Version Agitation/Aggression domain. Frequency of agitated behaviors was scored from one (rarely) to four (very often) and was multiplied by the severity of the behaviors with one (mild) to three (severe). Patients with dementia due to reasons other than Alzheimer's disease were excluded. Antidepressants were permitted concomitantly during the study if the drug and dose were stable 30 days before randomization and throughout the study. The CMAI score was assessed at screening, baseline, and then every two weeks during the 12-week study. At the end of the 12-week study period, no improvement was observed in symptoms of agitation with brexpiprazole compared with placebo. One limitation of the above RCTs was the variable dose of brexpiprazole, preventing adequate testing of the higher 2 mg dose which may have demonstrated symptom reduction. EBP

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In nursing home patients, which intervention is most effective in decreasing falls?

EVIDENCE-BASED ANSWER

In patients living in nursing homes, exercise interventions overall can reduce the numbers of falls by 27%, patients who fall by 20%, and recurrent fallers by 30%. Balance exercises (33% reduction) and long-term exercises (20% reduction) are more effective than control group interventions. Exercise combined with other interventions such as medication review and environmental modification can reduce the rate of falls and the number of fallers by 40% and 10%, respectively (SOR: **A**, meta-analyses of randomized controlled trials).

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In 2020, a meta-analysis including 36 randomized controlled trials (RCTs; N=30,057) focused on single, multiple, or multifactorial interventions for fall prevention.[1] The trials included nursing home residents with mean ages of 76.4 to 88.6 years old; the majority were female. Study duration ranged from six to 36 months, and intervention frequency ranged from two to seven times per week. Patients were randomized to receive no intervention or interventions including exercises (gait, balance, strength, resistance, flexibility, endurance, and functional training) of various types, frequencies, and durations; medication assessments (vitamin D supplementation and medication reviews); staff trainings (dementia, inappropriate drug prescriptions, fracture prevention, elder mistreatment, and fall preventions); and other therapies (urinary incontinence management, podiatry surgery/intervention, vision checks, and nutrition therapy). Outcomes included the overall number of falls, number of individuals who experienced falls (fallers), or number of recurrent fallers. Outcomes were assessed by nursing home staff, a fall diary, or medical records. Overall, fall prevention interventions reduced the numbers of falls (13 trials, N=16,134; risk ratio [RR] 0.73; 95% CI, 0.60–0.81), fallers (20 trials, N=9,962; RR 0.80; 95% CI, 0.72–0.89), and recurrent fallers (11 trials, N=3,192; RR 0.70; 95% CI, 0.60–0.81). Combinations of interventions that included exercise reduced the number of fallers (3 trials, N=2,434; RR 0.62; 95% CI, 0.39–0.97). Exercise interventions (5 trials, N=497; RR 0.64; 95% CI, 0.55–0.75) and staff education (3 trials, N=317; RR 0.70; 95% CI, 0.52–0.93) also reduced the number of fallers. Staff education reduced the number of recurrent fallers (6 trials, N=1,982; RR 0.60; 95% CI, 0.43–0.85). Multifactorial interventions that included fall risk assessments, medication review, environmental assessment, exercise, and staff education resulted in a reduction in the overall number of falls (7 trials, N=3,822; RR 0.65; 95% CI, 0.45–0.94). Limitations included differences in study design, variability of participant cognitive status, heterogeneity of interventions, and range of countries included in the studies.

In 2021, a meta-analysis including 14 RCTs (N=2,748) focused on exercise interventions for fall reduction.[2] The trials included nursing home residents, 73 years old and older (mean age 80 years old). Exclusions were residents who were not cognitively or physically able to participate in the interventions. Interventions included whole-body vibration, balance, strength, resistance training, flexibility, stretching, and exercise goal setting. The intervention durations varied between 4 weeks and 1 year, and the intervention frequency ranged from multiple times daily to one or two times per week. The number of falls were measured by self-report, a fall diary, or medical records. Overall, regular use of exercise reduced the likelihood of falls when compared with those who received no intervention (14 trials, N=2,748; RR 0.91; 95% CI, 0.88–0.93). Subgroup analyses indicated that balance exercises (2 trials, N=554; RR 0.67; 95% CI, 0.56–0.79) could reduce falls, as could long-term exercise (>6 months; 2 trials, N=2,035; RR 0.80; 95% CI, 0.65–0.98). The number of falls did not differ between those participating in complex (combination of multiple types of exercise) or short-term exercise versus the control group. Limitations included difficulty generalizing results given limited population representation, lack of blinding, various levels of existing

exercise in participants, heterogeneity of exercise, and the small number of studies included.

In 2017, a meta-analysis including 21 RCTs (N=5,540) focused on exercise interventions for fall reduction.[3] The trials included nursing home adults (65 years old and older, mean age 82.6 years old, 81% female). Interventions included exercise alone (strength, balance, endurance, or walking) or exercise combined with two or more other interventions including medication review, education, home visit, environmental modification, or staff education. The intervention duration was between 4 and 48 weeks. Outcome measures included the rates of falls and number of fallers and were assessed by nursing home staff or medical records. Overall, exercise interventions reduced the rate of falls (18 trials, N=5,047; RR 0.81; 95% CI, 0.68–0.97). Exercise combined with other interventions also resulted in a significant decrease in the rate of falls (14 trials, N=4,100; RR 0.6; 95% CI, 0.52–0.72) and the number of fallers (14 trials, N=4,100; RR 0.85; 95% CI, 0.77–0.95). Compared with control group interventions, all exercise interventions and exercise alone did not reduce the number of fallers, and exercise alone did not reduce the rate of falls. Limitations were similar to the previous study. EBP

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This clinical question was developed as an HDA through a standardized, systematic methodology with details described **here**.

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Is a shave biopsy inferior to excisional biopsy in the initial diagnosis of suspected melanoma?

EVIDENCE-BASED ANSWER

Shave biopsy results in a 42.9% rate of melanoma being present at the deep margin and 7.7% chance of inaccurate staging on initial biopsy, although with a low rate (2.3%) of change in the treatment plan (SOR: **B**, meta-analysis of cohort and cross-sectional studies). Excisional biopsies seem to have approximately a 3% to 4% higher sensitivity and specificity than shave biopsies (SOR: **B**, large retrospective cohort study).

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A 2021 meta-analysis of 14 cohort and cross-sectional studies (N=9,987) examined the impact of shave biopsy on staging and treatment of melanoma.[1] Patients' demographic data were not provided. Patients were included if they had a melanoma diagnosis regardless of stage. The number of patients who had shave biopsy, the number of patients with a positive deep margin after initial biopsy, the number of patients with a change in tumor stage after wide local excision (WLE), and the number of times the treatment recommendation changed after WLE were reported. Among studies reporting deep margin status after shave biopsy, 1,259 margins were positive after shave (11 studies, N=2,846; 42.9% positive, 95% CI, 27.8–58%; I^2=99%). Among studies reporting tumor staging after WLE, 145 melanomas were upstaged after WLE (8 studies, N=1,883; 7.7% upstaged, 95% CI, 4.6–10.8%; I^2=90%). Among studies reporting a change in treatment recommendation after WLE, 57 patients (8 studies, N=2,258; 2.3% treatment changed, 95% CI, 0.88–3.61%; I^2=84%) required additional treatments,

usually a larger WLE margin or sentinel lymph node biopsy. This study was limited by lack of patient demographic information. In addition, this study was not designed to directly compare shave biopsy with excisional biopsy.

A 2021 retrospective cohort study (n=3,668 biopsies) explored the clinical significance of initial biopsy type on accurate diagnosis of melanoma, comparing cases diagnosed by partial biopsy (majority shave or punch) with those diagnosed initially by excisional biopsy.[2] Patients' demographic data were not reported, but the source of included cases was referrals to the Victoria Melanoma Service (VMS) in Australia from 2014 to 2019. The VMS database was searched for cases of primary (not a metastatic lesion) cutaneous melanoma and specifics of each case including anatomical site; original biopsy method; including shave and elliptical excision; and if the original clinical diagnosis matched the final pathologic diagnosis. Biopsies were labeled as false negative if they failed to diagnose melanoma before confirmatory excision and labeled as false positive if internal pathology review led to an overturned diagnosis of melanoma. For shave biopsies, the false negative rate was 3.9% and the false positive rate was 8.9% (sensitivity 96.1% and specificity 91.1%). For primary excisional biopsies, the false negative rate was 0.8% and the false positive rate was 4.8% (sensitivity 99.2% and specificity 95.2%). This study was limited by lack of patient demographic information and unblinded internal pathology review. EBP

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Does the direct renin inhibitor aliskiren have any evidence of beneficial patient-oriented outcomes?

EVIDENCE-BASED ANSWER

No. Although supplementation with aliskiren, a direct renin inhibitor, does decrease n-terminal pro-brain natiuretic peptide (NT-proBNP) levels and renin activity in patients with New York Heart Association Classification II/III heart failure, it does not reduce cardiovascular mortality (SOR: **A,** systematic review and meta-analysis of randomized controlled trials [RCTs]). Aliskiren does not provide any additional renoprotective benefit in nondiabetic patients with chronic kidney disease stages 3 to 4 nor does it reduce clinically meaningful morbidity and mortality (SOR: **C,** small RCT of primarily disease-oriented outcomes).

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A 2018 systematic review and meta-analysis of five randomized controlled trials (N=1,973) conducted at a hospital's cardiology department compared heart failure (New York Heart Association Class II/III) treatment with aliskiren or matched placebo, using NT-proBNP and brain natiuretic peptide (BNP) levels, and mortality as primary outcomes.[1] Secondary outcomes included plasma renin activity and concentrations and serious adverse events. Aliskiren was given at doses of 150 and 300 mg once daily for six weeks to 12 months. All studies were considered to be of high quality (Jadad score ≥3). Aliskiren supplementation reduced NT-proBNP levels (standardized mean difference [SMD] –0.12; 95% CI, –0.21 to –0.03 pg/mL; $P=.008$) and plasma renin activity (SMD –0.66; 95% CI, –0.89 to –0.44 ng/mL; $P<.00001$) compared with control. However, no difference was observed in BNP levels, mortality rate, adverse events, or serious adverse events compared with the control group. Key limitations included use of only five randomized controlled trials (RCTs), two of which had a relatively small sample size (n <100). The short duration of the trials might not have been sufficient to detect meaningful outcomes for patients with heart failure.

In 2020, a small RCT (n=67) measured the renoprotective effects of aliskiren on patients with nondiabetic chronic kidney disease stages 3 to 4 (defined by an eGFR 15–59 mL/min/1.73 m^2 body surface area) at a teaching hospital in Hong Kong.[2] Thirty-seven patients (27 male, mean age of 55 years old) were given aliskiren (300 mg/d) added to the maximal tolerated dose of losartan (100 mg/d), and 39 patients (24 male, mean age of 55 years old) were given losartan alone. The primary outcome was a renal composite endpoint that included a doubling of baseline serum creatinine, 40% reduction in estimated glomerular filtration rate, end stage renal disease, or death. After 144 weeks, no differences were observed in the renal composite endpoint or cardiovascular events (including stroke, peripheral vascular disease, fatal and nonfatal infarction, and heart failure) between the two groups. The study was likely underpowered for the cardiovascular outcomes, raising the risk of type II error (falsely negative results). EBP

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The authors declare no conflicts of interest.
This clinical question was developed as an HDA through a standardized, systematic methodology with details described **here**.

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