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EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

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FPIN
Family Physicians Inquiries Network

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EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

STATEMENT OF PURPOSE

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

EDITORIAL POLICY

Statements and opinions expressed in articles and communications in this journal are those of the author(s) and not necessarily those of the editor, publisher, or any organizations endorsing this journal. The Publisher and editors of EBP do not endorse any methods, products, or ideas mentioned in the journal, and disclaim any liability which may arise from any material herein. Unless noted, authors have reported no competing interests and have nothing to disclose.

DISCLOSURE

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For patients with heart failure on a beta-blocker, is it safe to continue beta-blockers during a hospital admission for a CHF exacerbation?

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Case

A 67-year-old man with a history of hypertension and previous admissions for heart failure with reduced ejection fraction was admitted to the medicine ward with volume overload consistent with an acute heart failure exacerbation. His home medications include furosemide, lisinopril, and metoprolol. Should his beta-blocker be continued during his hospitalization?

Bottom Line

Do not stop. Discontinuation of beta-blockers in patients admitted to the hospital with acute heart failure is associated with increased mortality.

Review of Evidence

A 2015 systematic review and meta-analysis examined the effects of continuation versus withdrawal of beta-blockers in 2,554 patients with known heart failure (type not specified) admitted with acute decompensated heart failure.[1] The review included five observational studies and one randomized controlled trial published between 2000 and 2015. Included studies reported at least one of the following outcome measures: in-hospital mortality, short-term mortality (follow-up ranging from 60 to 180 days), or rehospitalization. In two studies that evaluated in-hospital mortality, discontinuation of beta-blocker therapy upon hospital admission was associated with significantly increased in-hospital mortality compared with continuation of beta-blocker therapy (2 studies; N=650; risk ratio [RR] 3.7; 95% CI, 1.5–9.1). Short-term mortality was significantly higher among patients whose beta-blocker was discontinued versus continued at admission (4 studies; N=2,051; RR 1.6; 95% CI, 1.0–2.5). Discontinuing beta-blockers was also associated with increased risk of the combined endpoint of rehospitalization or short-term mortality (4 studies; N=2,051; RR 1.6; 95% CI, 1.0–2.5). Significant heterogeneity was noted among the 4 studies (3 observation and 1 RCT) that evaluated the combined endpoint (I^2=77%). Another major limitation of the systematic review and meta-analysis was the retrospective nature of the majority of the studies included. Although data from the single RCT was included in all the analyses, the total number of patients (n=147) in the RCT was relatively small. In addition, the authors of the RCT noted that their trial was not adequately powered to look at the outcomes of death or rehospitalization[2].

A 2017 observational study examined the in-hospital, three-month, and 12-month mortality rates among 1,278 patients hospitalized with acute decompensated chronic heart failure (ADCHF) or acute decompensated de novo heart failure (ADNHF).[3] This trial included patient data from the Gulf aCute heArt failuRe registry (Gulf-CARE), a multinational multicenter prospective observational acute heart failure survey from seven Middle Eastern countries. Included patients had heart failure with reduced ejection fraction (left ventricular ejection fraction [LVEF] <40%) and were on a beta-blocker on admission. The study included 926 patients who continued beta-blockers during admission and 92 patients who discontinued beta-blockers. In patients with ADCHF, fewer in-hospital deaths occurred in patients who continued beta-blockers compared with those who discontinued beta-blockers (15 vs 37; odds ratio [OR] 0.05; 95% CI, 0.02–0.11). However, no significant difference was observed in three-month mortality when a multivariate logistic regression analysis was performed (OR 0.51; 95% CI, 0.23–1.1). In patients with ADNHF, fewer in-hospital deaths were noted in patients who continued beta-blockers compared with patients who discontinued beta-blockers (5 vs 17; P<.001), although mortality rates were comparable at three months and one year. Limitations as an observational study include possible selection bias: beta-blocker therapy may have been withdrawn in patients with more severe heart failure with a poor prognosis.

A 2007 secondary analysis of a randomized, double-blind, parallel-group trial examined mortality rates in patients with acute heart failure who had beta-blocker therapy discontinued, reduced, or continued at the time of their first postdischarge hospital follow-up visit.[4] This study did not meet the inclusion criteria of the above 2015 meta-analysis because it assessed the effect of both dose reduction and discontinuation on long-term outcomes (median follow-up=58 months). The trial included patients with symptomatic chronic heart failure (NYHA class II-IV) with LVEF <35% on optimal baseline therapy who had experienced at least one cardiovascular heart failure hospitalization during the two years before trial entry. Of the original 3,029 patients in the COMET trial, 752 met the inclusion criteria for the secondary analysis. Of those, 61 patients had beta-blockers discontinued, 162 had a dose reduction, and 529 were continued on the same dose at the visit after hospitalization. No significant mortality difference was noted between patients who discontinued or reduced beta-blocker therapy (58 vs 53%; hazard ratio [HR] 1.3; 95% CI, 0.9–2.0). All-cause mortality was lower in patients who continued the same beta-blocker dose compared with the combined reduction or withdrawal group (46% vs 57%; HR 1.6; 95% CI, 1.3–2.0). The mortality benefit of beta-blocker continuation persisted after adjusting for baseline variables (HR 1.3; 95% CI, 1.0–1.7). Because this was a post hoc or secondary analysis, when the beta-blocker dose change or discontinuation occurred (at admission, during hospitalization, or upon discharge) remains unknown.

Case Conclusion

Based on the best available evidence, the patient's beta-blocker was continued. His volume status improved with IV diuretics After two days in the hospital, he was discharged home without complication. Outpatient follow-up at three months showed that he was still taking his beta-blocker and had no further hospital admissions. EBP

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Weighted blankets for chronic pain, the jury is out

Baumgartner JN, Quintana D, Leija L, et al. Widespread Pressure Delivered by a Weighted Blanket Reduces Chronic Pain: A Randomized Controlled Trial. *J Pain*. 2022; 23(1):156-174. doi:10.1016/j.jpain.2021.07.009

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A double-blinded, active, placebo-controlled randomized trial conducted in 94 individual patients' homes during the COVID-19 pandemic evaluated the effect of patients' use of weighted blankets during sleep (47 patients in the 15-pound blanket group [15PG] vs 47 patients in the 5-pound blanket group [5PG]) on chronic pain. The inherent inability to blind patients in this trial led to the use of a five-pound blanket as the control. At the end of the study, 68% of participants were able to accurately guess they were in the control group and 62% accurately guess they were in the intervention group. The total trial period was seven days after a three-day wearing of just the fitness tracker without use of a blanket and a brief 15-minute session to get baseline data and demonstrate the use of data collection devices and blanket. The primary outcome was a change in chronic pain rating by visual analog scale (VAS) when comparing pre- and post-blanket use. Secondary outcomes included reduction of anxiety, improved sleep quality, and a reduction in Pain, Enjoyment of Life, and General activity Scale (PEG; a 3-item questionnaire with a scale of 3–30, with 10 as pain severely affecting life and activity). The patients were required to use proprietary software to provide informed consent and to complete online pre- and post-psychological assessments that collected PEG and the State Trait Anxiety Inventory (a 20-item scale that measures generalized, long-standing anxiety on a scale from 20 [low anxiety] to 80 [high anxiety]). Additionally, patients downloaded an Ecological Momentary Assessment (EMA) application (app) onto their smart phones; answered daily survey questions pushed from the app; wore a fitness tracker provided by the investigators and used the associated app to upload the fitness tracker data daily; and slept with the weighted blanket each night during the study. VAS questions on pain intensity, state anxiety, sleep quality, blanket-related pain expectation, blanket pleasantness, and blanket use were asked on the EMA app. The fitness tracker collected sleep data, estimated by movement and heart rate. Use of weighted blankets produced no statistically significant reduction in pain. Weighted blankets did not improve self-reported anxiety or sleep quality VAS scores. Sleep quality ratings were significantly lower on average in the 15PG compared with the 5PG (mean difference = –6.4; 95% CI, –12.70 to –0.11; P=.046). Tracker-collected data reflected significantly less deep sleep in the 15PG as well.

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	No	Clinically meaningful	No

Bottom line: The study did not show chronic pain reduction with use of weighted blankets generally. It did not enroll enough patients in each arm to satisfy the prestudy power analysis, and the investigators did not do an intention-to-treat analysis. The heavy weighted blankets group had significantly reduced quality of sleep.

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PCT-guided antibiotic therapy for sepsis

Kyriazopoulou E, Liaskou-Antoniou L, Adamis G, et al. Procalcitonin to Reduce Long-Term Infection-associated Adverse Events in Sepsis. A Randomized Trial. *Am J Respir Crit Care Med*. 2021; 203(2):202-210. doi: 10.1164/rccm.202004-1201OC

DOI 10.1097/EBP.0000000000001682

This pragmatic, real-world, multicenter randomized clinical trial evaluated the use of the predictive biomarker procalcitonin (PCT) to guide early discontinuation of antibiotic therapy in patients with sepsis in hopes of decreasing infection-associated adverse events. The trial took place in seven hospitals in Athens, Greece with 266 patients randomized 1:1 to the PCT-guided intervention or the standard of care (SOC), the 2016 international guidelines for the management of sepsis and septic shock from the "Surviving Sepsis" campaign.[1] Patients included those with sepsis as defined by the sequential organ failure assessment score of ≥2 and infections such as pneumonia, pyelonephritis, or bacteremia.[2] Patients with pregnancy, lactation, HIV infection with a low CD4 count, neutropenia, cystic fibrosis, and those with viral, parasitic, or tuberculosis infections were excluded from participation. Of note, all patients were managed on general medical wards and not in intensive care units.

Researchers collected serum PCT samples at baseline and then at day 5 of therapy. Discontinuation of antibiotic therapy in the PCT trial arm occurred once PCT levels were ≤0.5 mcg/L or dropped by at least 80%. If PCT levels did not meet one of these criteria, the laboratory examinations would be repeated daily, and antibiotic therapy would continue until the rule was met. Neither patients nor investigators were blinded to the treatment assignments, but investigators in the SOC arm were kept unaware of day 5 PCT results. In the PCT arm, 71% met day 5 criteria for stopping antibiotics, and upon retrospective analysis, a near-identical 70% in the SOC arm would also have met the same criteria.

An assessment of stool colonization with either *Clostridium difficile* or multidrug-resistant organisms (MDROs) was done by stool cultures at baseline and at days 7, 28, and 180.

The primary outcome of infection-associated adverse events was evaluated at 180 days and was defined as new cases of *C difficile* or MDRO infection or death associated with baseline infection with either *C difficile* or MDROs. Of the 133 participants allocated to each trial arm, eight withdrew consent before treatment in the intervention group and two withdrew in the SOC group, with the remaining 125 and 131 participants, respectively, completing the interventions and not lost to follow-up.

Through intention-to-treat analysis, nine patients (7.2%; 95% CI, 3.8–13.1%) in the PCT group compared with 20 patients (15.3%; 95% CI, 10.1–22.4%) in the SOC group experienced the primary outcome of an antibiotic-associated adverse event at 180 days, resulting in a hazard ratio (HR) of 0.45 (95% CI, 0.2–0.98; a notably wide, albeit significant CI).

Secondary outcomes also favored the RCT arm in 28-day mortality (19 vs 37 patients; hazard ratio 0.51; 95% CI, 0.29–0.89), median length of antibiotic treatment (5 days in the PCT group vs 10 in the SOC group; $P<.001$), and median hospitalization cost (€957 in the PCT group and €1,183 in the SOC group; $P=.05$).

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, PubMed, and the Society of Critical Care Medicine's website with the terms "sepsis," "procalcitonin," and "adverse events" to find additional literature to place this research into the context of current clinical practice.

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

Bottom line: This pragmatic, real-world trial demonstrates that the biomarker procalcitonin proves beneficial in decreasing infection-associated adverse events in patients hospitalized on a general medical ward. Additionally, although previous trials demonstrated utility in guiding antibiotic therapy in patients with lower respiratory tract infections, this trial expanded utility to patients with sepsis and pneumonia, pyelonephritis, or bacteremia. One caveat with the results regards the very wide (but significant) CI for the hazard ratio, suggesting greater uncertainty and less precision in the chance of obtaining improved outcomes but reassurance that outcomes should not be worse with PCT-directed therapy.

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Among patients who have had a stroke, are pharmacological interventions effective for preventing depression?

EVIDENCE-BASED ANSWER

In patients with recent ischemic or hemorrhagic stroke, pharmacological therapy is effective in preventing poststroke depression compared with placebo (SOR: **A**, 2 meta-analyses of randomized controlled trials and expert consensus).

DOI 10.1097/EBP.0000000000001607

A 2020 systematic review and meta-analysis of 19 randomized controlled trials (RCTs; N=1,771) examined the effects of pharmacological and non-pharmacological preventive treatments on the development of poststroke depression (PSD).[1] Patients were male and female around 65 years old with a history of ischemic or hemorrhagic stroke who were not depressed before their stroke. Pharmacological treatments included multiple classes of medications including selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) with fluoxetine, sertraline, escitalopram, and paroxetine being the most common treatments. Treatment regimens varied between trials and included fixed, flexible, or escalating dosing compared with placebo over a median of 12 weeks. Diagnosis of depression was assessed through multiple validated assessment scales, most commonly the Hamilton Depression Rating Scale and the Hospital Anxiety and Depression Scale, and cutoff scores were pooled. After pooling nine (N=734) antidepressant trials, patients were less likely to develop depression when treated with an antidepressant compared with placebo (risk ratio [RR] 0.50; 95% CI, 0.37-0.68). Five trials used SSRIs, two trials used TCAs, one trial used an SNRI, and one trial used an antidepressant no longer in use (indeloxazine hydrochloride). No significant harms were found. Limitations included wide confidence intervals and a high level of dropout (20% or higher) in trials.

A 2020 meta-analysis of 10 RCTs (N=5,370) compared early SSRI therapy with placebo in the prevention of PSD.[2] A subgroup analysis of four trials (N=3,768) able to be pooled for incidence of PSD was identified. Patients were adults with stroke onset less than 1 month before treatment or placebo initiation. SSRIs included sertraline 50 mg per day (two trials, N=248), escitalopram scaled dosed (one trial, n=405), and fluoxetine 20 mg per day (one trial, n=3,127) for 3 to 6 months. Depression occurrence was assessed using validated scales such as the Hospital Anxiety and Depression Scale, the Hamilton Depression Rating Scale, and the Montgomery–Asberg Depression Rating Scale. Patients in the SSRI group were significantly less likely to experience a depression compared with placebo groups (RR 0.78; 95% CI, 0.67-90). One key limitation was the lack of safety and adverse event data available for analysis.

A 2017 American Heart Association/American Stroke Association evidence-based scientific statement suggested that pharmacological treatment may be effective preventing PSD (no recommendation strength given).[3] The association did note that all studies excluded patients with aphasia and significant cognitive impairment, limiting the generalizability of the recommendation. EBP

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Do epidural corticosteroid injections provide any benefit in patients with lumbar radiculopathy?

EVIDENCE-BASED ANSWER

For patients with lumbar radiculopathy, epidural corticosteroid injections (ESIs) provide slight (ie, ~5–15%) improvement in leg pain for up to three months, but not longer, when compared with placebo injections (SOR: **A**, systematic review and meta-analysis of randomized controlled trials [RCTs]). ESIs are associated with minimal (ie, <5%) functional improvement (SOR: **A**, systematic review and meta-analysis of RCTs). Guidelines recommend ESIs be considered as part of a multimodal treatment plan for short-term pain relief but are mixed regarding the long-term benefit of ESIs in patients with low back pain and radicular symptoms (SOR: **C**, evidence-based guidelines with inconsistent recommendations).

DOI 10.1097/EBP.0000000000001671

A 2020 systematic review of 25 randomized controlled trials (RCTs; N=2,470) examined the efficacy and safety of epidural corticosteroid versus placebo injections on pain and disability in patients with lumbosacral radicular pain.[1] Studies were mainly conducted in Europe (14 RCTs, N=1,304), North America (6 RCTs, N=638), and Asia (3 RCTs, N=369). Patients' mean ages ranged from 37.3 to 52.8 years old. Lumbosacral radicular pain was defined clinically, and several syndromes were included as synonyms, such as nerve root entrapment, radiculitis, and sciatica. No restriction was noted on the duration of symptoms. Corticosteroids used in the trials were 40 to 80 mg of methylprednisolone acetate (16 RCTs, N=636), 10 to 80 mg of triamcinolone acetonide (6 RCTs, N=334), 3 to 6 mg of betamethasone (3 RCTs, N=180), 15 mg of dexamethasone (1 RCT, n=52), and 50 mg of prednisolone acetate (1 RCT, n=47). Injections were performed with (9 RCTs) or without (15 RCTs) imaging guidance, by interlaminar (13 RCTs), caudal (6 RCTs), and transforaminal (6 RCTs) approaches. Placebo was defined as an inert substance (ie, one with no pharmacological activity such as normal saline), or a pharmacologically active substance not considered to provide sustained benefit (eg, local anesthetic), and was injected either into the epidural space (17 RCTs) or into the adjacent spinal tissue (8 RCTs). Primary outcomes were self-reported leg pain intensity (by visual analogue or numerical scale) and disability (by questionnaire). For pain intensity, outcome measures were converted to a common 0 to 100 scale to calculate the mean differences (MDs) of pooled effects. For disability, because trials used different instruments, authors calculated a standardized MD and transformed this into an MD expressed on a 0 to 100 scale to facilitate interpretation. Authors considered a clinically important difference for most people to be a mean between-group difference greater than 10%. Outcome data were grouped into four time points: immediate (≤2 weeks), short term (>2 weeks but ≤3 months), intermediate term (>3 months but <12 months), and long term (≥12 months). Epidural corticosteroid injections (ESIs) were marginally more effective than placebo in reducing leg pain at immediate (1 RCT, n=158; MD –15.0; 95% CI, –25.9 to –4.1) and short-term (8 RCTs, N=949; MD –4.9; 95% CI, –8.8 to –1.1) follow-up, but not at intermediate-term (1 RCT, n=158; MD 9.1; 95% CI, –1.4 to 19.6) or long-term (3 RCTs, N=453; MD –0.35; 95% CI, –6.2 to 5.5) follow-up. Disability was slightly reduced at short-term (12 RCTs, N=1,367; MD –4.2; 95% CI, –6.0 to –2.2) and intermediate-term (6 RCTs, N=866; MD –3.1; 95% CI, –6.2 to –0.15) follow-up, but not at immediate (2 RCTs, N=243; MD 1.2; 95% CI, –2.6 to 5.1) or long-term (7 RCTs, N=882; MD –2.2; 95% CI, –5.9 to 1.6) follow-up. The overall quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and was deemed very low to moderate.

A 2018 evidence-based guideline from the Institute for Clinical Systems Improvement on the management and treatment of acute or subacute low back pain recommended that ESI may be used as an adjunctive treatment for short-term pain relief in patients with acute (<4 weeks) or subacute (4–12 weeks) low back pain with radiculopathy (strong recommendation based on moderate-quality evidence).[2] The guideline noted that the evidence supporting ESI for low back pain with radiculopathy was conflicting, and that ESI should be offered after an appropriate treatment course of

conservative therapy and should not be used as monotherapy.

A 2017 evidence-based clinical practice guideline from the U.S. Department of Veterans Affairs and the U.S. Department of Defense regarding the diagnosis and management of low back pain recommended against ESI for long-term reduction of radicular low back pain (strong recommendation against, based on the GRADE methodology).[3] The guideline recommended offering ESI for very short-term (≤2 weeks) reduction of radicular low back pain (weak recommendation for, based on the GRADE methodology).

A 2021 evidence-based guideline from the American Society of Interventional Pain Physicians on epidural interventions in the management of chronic spinal pain recommended caudal, interlaminar, or transforaminal fluoroscopically guided epidural injections, with or without corticosteroids, to provide long-term benefit for patients with disc herniation and radicular symptoms (strong recommendation based on multiple moderate- to high-quality trials).[4] EBP

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In neonates, is a history of maternal tetrahydrocannabinol use compared to no maternal tetrahydrocannabinol use associated with increased incidence of NICU admission?

EVIDENCE-BASED ANSWER

Yes. Maternal marijuana use during pregnancy is associated with an increased likelihood of NICU admission (SOR: **B**, meta-analysis of cohort studies). Maternal marijuana use is associated with increased composite neonatal morbidity or death (SOR: **B**, retrospective cohort study). As always, associations are not proof of causation.

DOI 10.1097/EBP.0000000000001659

A 2016 systematic review and meta-analysis of 24 retrospective cohort, case–control, and observational studies (N=126,166) examined correlations between prenatal marijuana use and maternal and child health outcomes.[1] Four of the 24 studies included in the meta-analysis addressed NICU admission. Study participants were pregnant women 14 to 44 years old, of various races and ethnicities, who self-reported cannabis use or had a positive urine toxicology test for cannabis. Rates of marijuana use across studies were 0.006% to 27%. Patients using other drugs were excluded. Infants were compared to infants whose mothers did not use cannabis during pregnancy. Infants exposed to cannabis in utero were more likely to need NICU placement compared with infants of mothers who did not use cannabis

during pregnancy (4 studies, N=39,026, odds ratio [OR] 2.02; 95% CI, 1.27–3.21, I^2=78%). Exposure to cannabis in utero was also associated with a low birth weight (7 studies, N=49,049, adjusted OR 1.77; 95% CI, 1.04–3.01, I^2=89%). This meta-analysis had several limitations, including relying on maternal self-report of cannabis use and not excluding the potentially confounding effects of maternal tobacco and alcohol use.

A 2019 retrospective cohort study of 661,617 pregnant women looked at the effects of prenatal cannabis exposure on maternal, perinatal, and neonatal outcomes.[2] Women who delivered a singleton infant >20 weeks' gestational age at a hospital in Ontario between 2012 and 2017 were included. The mean age of mothers was 30 years old; mothers <15 years old were excluded. The mean gestational age of their neonates was 39.3 weeks. Cannabis use during pregnancy was reported by 9,427 women (1.4% of sample) at their first prenatal visit and while being admitted to labor and delivery. These women were compared with women who did not report cannabis use. Matching was used to control for differences in obstetrical and socioeconomic data between cannabis users and nonusers. The primary endpoint of the study was preterm birth (birth before 37 weeks). Mothers who used cannabis were more likely to experience preterm birth (12% vs 6%, RR 1.41; 95% CI, 1.36–1.47). Maternal cannabis use was also associated with increased incidence of transfer to NICU (19% vs 14%, RR 1.40; 95% CI, 1.36–1.44). Study limitations included cannabis use being based on self-report and lack of quantification of cannabis exposure.

A 2017 secondary data analysis of the Stillbirth Collaborative Research Network dataset (N=1,610) looked at the relationship between maternal marijuana use and perinatal complications.[3] The 2014 Stillbirth Collaborative Research Network dataset examined the association between stillbirth and maternal marijuana use, as defined by the presence of tetrahydrocannabinol in the umbilical cord homogenate.[4] The original study found an increased risk of stillbirth in babies with tetrahydrocannabinol in the umbilical cord sample (OR 2.34; 95% CI, 1.13– 4.81), although the effect was partially confounded by maternal tobacco use. Participants in the 2017 study included live-born infants from singleton gestations ≥24 weeks from multiple locations in the United States. Infants were excluded if their mothers had missing obstetrical or substance use history or if they were born with anomalies. In the study population, 2.7% of the infants were exposed to cannabis in utero (1.6% by mother's self-report and 1.9% by tetrahydrocannabinol in umbilical cord homogenate). These infants were compared with infants who were not exposed to cannabis in utero and had similar clinical, socioeconomic, and tobacco exposures. Outcomes were measured by analysis of the original dataset, which was obtained through chart review, maternal interviews, and laboratory tests. Maternal marijuana use was not associated with a statistically significant increase in NICU admission (17% vs 9.5%, P=.12) but was associated with increased composite neonatal morbidity (pulmonary morbidity, necrotizing enterocolitis, seizures, retinopathy of prematurity, infection morbidity, anemia requiring blood transfusion, neonatal surgery, hyperbilirubinemia, and neurological morbidity) or death after adjustment for tobacco, other illicit drug use, and race (adjusted OR 3.11; 95% CI, 1.4–6.9). Study limitations included small sample size, overall low rate of marijuana use, and poor agreement between self-reported cannabis use and tetrahydrocannabinol in umbilical cord homogenate. EBP

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Should patients taking direct oral anticoagulants be routinely monitored with coagulation studies?

EVIDENCE-BASED ANSWER

No. Patients taking fixed doses of direct oral anticoagulants (DOACs) without routine coagulation monitoring have reduced overall stroke or systemic embolic events, all-cause mortality, intracranial hemorrhage, and hemorrhagic stroke, but increased gastrointestinal bleeds compared with patients taking international normalized ratio (INR)-adjusted warfarin (SOR: **A**, meta-analysis of phase 3 clinical studies). Routine coagulation studies do not strongly correlate with therapeutic DOAC serum concentrations (SOR: **C**, observational study using non–patient-oriented outcomes).

DOI 10.1097/EBP.0000000000001593

A 2014 meta-analysis of four phase 3 randomized clinical studies (N=71,683) evaluated the incidence of overall stroke and systemic embolic events, ischemic stroke, hemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial hemorrhage, and gastrointestinal bleeding in patients with atrial fibrillation taking warfarin (29,272) or direct oral anticoagulants (DOACs; 42,411).[1] Thirty-eight percent of patients were >75 years old, 38% were women, 19% had a creatinine clearance <50 mL/min, 77% had persistent or permanent atrial fibrillation, 30% had prior stroke or transient ischemic attack (TIA), and 34% were on ASA at baseline. DOACs included in this meta-analysis were dabigatran 110 and 150 mg twice daily, rivaroxaban 20 mg daily, apixaban 5 mg twice daily, and edoxaban 30 and 60 mg daily. All DOACs were given at fixed dosing with no routine laboratory monitoring. In patients taking warfarin, average individual time in therapeutic INR range over all three trials was 65%. When compared with warfarin, DOACs reduced overall stroke or systemic embolic events (relative risk [RR] 0.81; 95% CI, 0.73–0.91), all-cause mortality (RR 0.90; 95% CI, 0.85–0.95), intracranial hemorrhage (RR 0.48; 95% CI, 0.39–0.59), and hemorrhagic stroke (RR 0.49; 95% CI, 0.38-0.64), but increased gastrointestinal bleeding (RR 1.25; 95% CI, 1.01–1.55). No difference was noted in major bleeding events (RR 0.86; 95% CI, 0.73–1.00), ischemic stroke (RR 0.90; 95% CI, 0.83–1.02), and myocardial infarction (RR 0.97; 95% CI, 0.78–1.20). Study limitations include that DOACs were grouped together rather than compared relative to each other and to warfarin, and that data collected from clinical trials that often included healthier patients may affect generalizability. In addition, several authors of this meta-analysis had industry ties.

A 2016 observational multiplatform study (n=635) looked at the responsiveness of prothrombin time (PT) and activated thromboplastin time (APTT) to DOAC concentrations in patients with atrial fibrillation.[2] Patients were from four different clinics and were prescribed dabigatran, rivaroxaban, or apixaban for anticoagulation with drug and dose chosen by the attending physician. Patients were followed their first month on the anticoagulants. Each patient had a peak sample taken two hours after DOACs ingestion, as well as a trough sample taken 12 hours after the last dose of dabigatran or apixaban or 24 hours after rivaroxaban. The samples were analyzed using PT and APTT coagulation studies as well as diluted thrombin time (dTT) and anti-FXa assays to assess DOAC anticoagulant activity (expressed as drug concentration equivalent in nanograms per milliliter). The extent of prolongation of PT and APTT was compared with increasing DOAC concentrations using linear regression. Researchers derived correlation coefficients (r-values) and coefficients of determination (r^2-values) from the regression lines to describe the relationship between the coagulation studies and DOAC concentrations using both trough and peak blood samples. For apixaban, the correlation between the anti-FXa assay and PT was r=0.81 to r=0.54; however, PT was still within normal limits when apixaban concentrations were elevated at 151 to 170 ng/mL (clinic A) and 231 to 250 ng/mL (clinic B). Dabigatran had a correlation between APTT and dTT ranging from r=0.80 to r=0.62, but APTT was still within normal limits when dabigatran concentrations were elevated at 51 to 70

ng/mL (clinics A, B, and C) and 131 to 150 ng/mL (clinic D). Rivaroxaban's correlation between the anti-FXa assay and PT ranged from r=0.91 to r=0.73, but PT was still within normal limits when with rivaroxaban concentrations of 91 to 110 ng/mL (clinic A), 51 to 70 ng/mL (clinic B), and 171 to 190 ng/mL (clinic D). Overall, the slopes of the regression lines were relatively small, showing that the PTT and APTT were not particularly responsive to DOAC concentration. This observational study was limited by not using gold standard methods to assess DOAC concentrations and that the laboratories were spread across four different facilities, allowing for variability in reagents and coagulometers used. EBP

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Are there effective interventions that decrease suicidality in primary care settings?

EVIDENCE-BASED ANSWER

Multifaceted collaborative care approaches with care managers in the primary care setting decrease suicidal ideation and incidence when compared with standard treatment in older patients (SOR: **A**, systematic review [SR] of randomized controlled trials [RCTs]). Brief cognitive behavioral therapy for insomnia (bCBTi) may reduce suicidal ideation (SI) intensity in patients with major depressive disorder or posttraumatic stress disorder (SOR: **C**, small RCT). Biweekly brief cognitive behavioral therapy (bCBT) reduces the frequency of suicidal ideation in veterans with chronic illnesses (SOR: **B**, cohort study).

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A 2017 systematic review looked at interventions to prevent suicidal behaviors and reduce suicidal ideation in individuals >65 years old.[1] Four randomized controlled trials (RCTs) included 40,870 elderly patients and looked at primary care–based interventions. Two of the four studies, with 17,732 patients, used Prevention of Suicide in Primary Care Elderly: Collaborative Trial intervention, a collaborative physician/care manager approach to providing treatment per guidelines, monitoring clinical status, and providing follow-up. Physicians in the comparison group provided usual care. The study durations were 12 and 24 months, respectively. The Scale for Suicidal Ideation (SSI) was used to evaluate participants and an SSI score >0 indicated current suicidal ideation. At eight months, 70.7% of patients in the intervention group had resolution of suicidal ideation compared with 43.9% of those receiving usual care (P=.005). The second study described suicidality by one of three descriptions: "passive suicidal desire," "active suicidal desire," and "preparation." By four months, suicidality was reduced by 12.8% in the intervention group and 3.0% in the control group (P=.02). The third study included 1,801 patients diagnosed with major depression or dysthymia by DSM-4 criteria and followed them over one year. The study used Improved Mood Promoting Access to Collaborative Care Treatment intervention, a collaborative approach where

depression care managers worked in the patient's primary clinic to support physicians. Patients in the comparison group were given usual care. SI was defined by patients reporting "thoughts of ending your life" on the Hopkins Symptoms Checklist. The intervention group demonstrated decreased SI at 6, 12, 18, and 24 months, with the largest difference being 9.8% versus 15.5% at 12 months (OR 0.54; 95% CI, 0.40–0.73; $P<.001$). A fourth study of 21,762 patients over 60 years old involved a Depression and Early Prevention of Suicide in General Practice intervention, in which 373 physicians in the experimental group were educated on the assessment and management of depression, a practice audit of 20 patients was performed with feedback, and a newsletter was given about the progress of the study. The comparison group physicians only received information about the study and a picture of the interventions used. Over 24 months, intervention substantially decreased SI and suicidal attempts (OR 0.80; 95% CI, 0.68–0.94). A meta-analysis was not performed.

A 2019 double-blind RCT investigated whether bCBTi in primary care settings reduced suicidality and included 54 English-speaking patients 8 to 70 years old who were diagnosed with major depressive disorder (MDD) or posttraumatic stress disorder (PTSD) and had SI[2]. The study compared bCBTi with treatment-as-usual (TAU). Participants in the TAU group received treatment for MDD or PTSD as recommended by treatment providers along with pharmacotherapy for insomnia. Patients in the bCBTi group received four sessions of bCBTi instead of pharmacotherapy for insomnia. At the end of six weeks, suicidal ideation intensity was measured by the Columbia-Suicide Severity Rate Scale (C-SSRS). Depression severity was also assessed using the Patient Health Care Questionnaire 9 (PHQ-9). Patients receiving bCBTi had no change in SI intensity (effect size [ES]=–0.26; 95% CI, –0.81 to 0.30). However, bCBTi had a large lowering effect of PHQ-9 scores (ES= -1.16; 95% CI, -1.7 to -0.56), which included questions regarding suicidality.

A 2019 secondary analysis of data from a previous RCT trial looked to find out if bCBT in the primary care setting reduced suicidality and included 302 veterans with congestive heart failure or COPD who screened positive for depression or anxiety symptoms using the Beck Anxiety Inventory (BAI) or the Patient Health Questionnaire 9 (PHQ-9)[3]. The study compared bCBT with enhanced usual care (EUC). For the EUC group, study staff recommended their symptoms of depression and anxiety be addressed as part of their routine care. Patients in the bCBT group received weekly or biweekly sessions that included techniques on use of coping statements, behavioral activation, relaxation, and adaptations specific to their physical health conditions. Suicidal ideation was assessed using item nine of the PHQ-9 (thoughts you would be better off dead or of hurting yourself) at baseline and again at four, eight, and 12 months. Patients in the bCBT group were less likely to endorse suicidal ideation than those in the EUC group at four months (mean difference [MD] –1.27 points; 95% CI, -2.0 to -0.5; odds ratio [OR]=0.28; $P=.001$) and eight months (MD –1.14 points; 95% CI, –2.0 to –0.3; OR=0.32; $P=.006$) but not at 12 months. EBP

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In infants with latch or feeding difficulties, does frenulectomy improve outcomes?

EVIDENCE-BASED ANSWER

Infant frenulectomy reduces maternal nipple pain by approximately 10% and increases both the subjective quality of latch and mother's assessment of breastfeeding effectiveness. However, it does not seem to improve objective breastfeeding measures (SOR: **B**, meta-analysis of lower quality randomized controlled trials [RCTs] and systematic review of RCTs and cohort trials). No consensus exists on diagnostic criteria or indications for frenulectomy regarding infant and maternal factors.

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A 2017 Cochrane review evaluated the safety and effectiveness of frenulectomy to improve feeding ability among infants with tongue-tie. Five randomized controlled trials were included in the review (N=302) that compared frenulectomy versus no frenulectomy or frenulectomy versus sham procedure in newborn infants. Studies excluded were either not randomized control trial (RCT) or compared different interventions. Included studies evaluated infants with confirmed tongue-tie, breastfeeding difficulties, and maternal nipple pain. No adverse events were reported after the procedure (excessive bleeding, infection, other local damage). An analysis of two studies (N=155) showed no change after the procedure on the 10-point LATCH feeding scale (higher scores equate to better breastfeeding) (mean difference [MD] –0.07; 95% CI, –0.63 to 0.48; *P*=.88), whereas a third study (N=58) did show improvement on the 12-point Infant Breast Feeding Assessment Tool scale, with higher scores indicating better breastfeeding behaviors (MD 3.5; 95% CI, 3.06–3.94). Of note, this third study only evaluated infants with a severe tongue-tie (based on Hazelbaker Assessment Tool for Lingual Frenulum Function scale). Four studies assessed maternal pain, all of which showed a reduction in maternal pain though using different pain scales (MD –0.74; 95% CI, –1.35 to –0.13 on 10-point visual analog pain scale, MD –8.6; 95% CI, –9.37 to –7.83 on Short-Form McGill Pain Questionnaire, scoring range 0–78). These studies all had shortcomings including small sample size and poor blinding. Furthermore, all study controls were offered frenulectomy with most of controls eventually undergoing the procedure. No study demonstrated that frenulectomy led to long-term successful breastfeeding.[1]

A 2019 systematic review evaluated 20 studies that compared symptoms of problematic breast feeding before and after frenulectomy. Inclusion criteria were studies conducted on children birth to 12 months old, published in English, with a full-text option available to the researchers. Exclusion criteria were not original research, case reports with less than three patients, age >12 months, studies that did not record both preprocedure and postprocedure data, did not measure feeding, or had another anatomical variant other than tongue-tie. The study objective was to evaluate the outcomes after frenulectomy. Second, the study sought to evaluate the assessment tools used in the diagnosis and procedure indications. Of studies included, four were randomized control trials (included in the Cochrane review) and the rest a combination of retrospective and prospective cohort studies. Sample size ranged from 14 to 246 (median 58). After frenulectomy, mothers generally reported improvement in the quality of breastfeeding, specifically noting short-term improvements in maternal nipple pain (improved in 19 studies immediately and up to two weeks postprocedure), latch, and feeding duration. The review did not identify a best diagnostic comprehensive feeding assessment tool to determine which patients would benefit most from frenulectomy. Limitations in these studies included difficulty measuring objective improvement postprocedure or attributing this improvement to frenulectomy because it is expected most measures will improve with time and experience.[2]

A 2020 prospective cohort study evaluated 343 infants for improvement in breastfeeding who were referred to an outpatient otolaryngology clinic for evaluation of ankyloglossia. The Coryllos classification was used to determine the degrees of ankyloglossia, if present. This classification system grades ankyloglossia from type 1 to type 4 with type 4 being the most severe. This study evaluated the effect of frenulectomy from the mother's perspective, filling out questionnaires before consultation, at one week, and three months after procedure.

Three hundred fourteen patients underwent frenulectomy and 29 did not. The strongest associated factor with those who did not undergo frenulectomy was older age (16 vs 27 days). At one week, 123 patients were lost to follow-up. Of the remaining patients, approximately 66% reported improvement of symptoms (ranging from mild to marked), whereas 17% were no longer breastfeeding and 13.6% were still having weight gain problems. At three months, only 96 patients followed-up, with 19% not breastfeeding, 20% with no subjective improvement, and 64% with improvement from mild to marked. When compared with the expected improvement from the consulting specialist, no difference existed ($P=.08$). Limitations included selection bias and high drop-out rate, and difficult follow-up, given the anonymous nature of study.[3] EBP

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Does stroke-specific telemedicine (telestroke) decrease the mortality rate in patients with strokes?

EVIDENCE- BASED ANSWER

No. Stroke-specific telemedicine is not associated with a decrease in mortality when compared with in-person medicine. In patients with stroke, both in-hospital and 90-day mortality rates for telemedicine are noninferior to in-person medicine (SOR: **A**, meta-analysis of randomized controlled trials and cohort studies and additional cohort study).

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A 2018 meta-analysis of 26 studies, consisting of two randomized controlled trials (RCTs) and 24 observational cohort studies (N=6,605), examined the effectiveness of telestroke compared with an in-person standard of care on treatment times and clinical outcomes of acute stroke care.[1] Patients had a mean age ranging from 62.5 to 80 years old with 32% to 66% of male in the telestroke arms and mean ages of 60.1 to 78 years old with 32% to 63% of male in the control arms. Patients who had acute ischemic stroke with a National Institute of Health stroke score (NIHSS) of 4 to 24 and a perfusion/diffusion mismatch on brain imaging were included. The NIHSS, which ranges from 0 to 42 with lower score indicating less stroke-related deficits, was used to evaluate language, neglect, motor strength, ataxia, dysarthria, level of consciousness, extraocular movement, visual-field loss, and sensory loss. Interventions were telestroke-based systems (telephone, videoconferences, or teleradiology), as compared with bedside (face-to-face) acute stroke care at a stroke center with 24-hour access to thrombolysis and stroke experts. Outcomes were mortality, symptomatic intercranial hemorrhage (defined as CT-confirmed intercranial hemorrhage with a rise of ≥4 points on the NIHSS), favorable clinical outcome (reduction of ≥4 points on NIHSS), length of hospital stay (days), discharge destination (home vs rehab), and onset-to-treatment time (minutes). In-hospital mortality of in-person care compared with telestroke was similar (18 studies, N=4,907; odd ratios [OR] 1.21, 95% CI, 0.98–1.49; $I^2=0\%$). Mortality at 90 days was also similar (9 studies, N=3,193; OR, 1.08, 95% CI, 0.85–1.37; $I^2=0\%$). The effect estimate for symptomatic intercranial hemorrhage did not favor either group (21 studies, N=4,022; OR, 1.10, 95% CI, 0.79–1.53; $I^2=0\%$).

Regarding onset-to-treatment time, no significant difference was detected between telestroke and control groups (20 studies, N=4,430; mean difference, –5.9 minutes, 95% CI, –13.23 to 1.42; I^2=84%). No significant differences were observed in favorable clinical outcomes at discharge (5 studies, N=1,475; OR 1.03, 95% CI, 0.69–1.53; I^2=54%) and 90 days later (11 studies, n=3,022; OR 0.99, 95% CI, 0.82–1.81; I^2=0%) between the two arms (HDA, Methods, Supplemental Digital Content 1).

A 2018 prospective cohort study (n=1,000) assessed the quality of telestroke care in patients with AIS as compared with in-person stroke care.[2] Patients were at least 18 years old with acute ischemic stroke from Mayo Clinic Hospitals in multiple locations (n=500) and a Mayo Clinic–affiliated telestroke hospital (n=500). The median age of patients was 74 years old, and 57% were male. The primary outcome was the percentage of accurate decision-making for eligibility of IV alteplase therapy as assessed by blinded adjudication. The secondary outcomes included IV alteplase administered, postthrombolysis symptomatic intercranial hemorrhage, favorable outcome (the NIHSS: 0–1), death, VTE prophylaxis, antithrombotic therapy administered by end of hospital day 2, discharged on anticoagulation, discharged on cholesterol-reducing treatment, assessed for or received rehabilitation services during hospitalization, length of stay for initial acute care hospitalization, and time from stroke alert activation to start of treatment. No significant difference correctly identifying patients for IV alteplase was observed between the telestroke care and in-person stroke groups (telestroke care 96%, 95% CI, 94–97% vs in-person care 97%, 95% CI, 95–98%; *P*=.032). No significant difference was observed in mortality (5.4% for telestroke care vs 3.8% for in-person care; *P*=.25) between the two groups. The other secondary outcomes were inferior when no in-person care was observed as compared with the presence of the stroke team and evidence-based measures in place. This study was limited by sample size, unspecific timeline, and lack of follow-up data. EBP

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Is consumption of artificially sweetened beverages associated with obesity in adults?

EVIDENCE-BASED ANSWER

Observational studies suggest that consumption of artificially sweetened beverages is associated with a small increase in the risk of obesity in adults (SOR **B**: systematic reviews of prospective cohort studies with inconsistent findings). However, experimental studies indicate artificial sweeteners may be weight-neutral when compared with water or placebo and are associated with moderate weight loss when compared with sucrose sweeteners (SOR **B**: systematic reviews of low-quality randomized controlled trials).

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A 2020 systematic review and meta-analysis of six prospective cohort studies (N=26,551) assessed the association between artificial sweetened beverage consumption and obesity.[1] The studies included adult patients (age range 25–84 years old at baseline) who were recruited for population-based, multicenter trials or single-city trials in Denmark, Spain, and the United States. The studies asked patients to report on their dietary habits, and the

median follow-up was 6.75 years. The review did not give detailed information about the types of artificial sweetened beverages consumed. Obesity status (body mass index [BMI] ≥30 kg/m^2 or waist circumference >102 cm for men and >88 cm for women) was self-reported in two studies (N=18,336) and measured by investigators in the other four (N=8,215). In a dose-response meta-analysis, the risk of obesity increased 20% for each 250 mL of artificial sweetened beverage consumed per day (5 trials, N=22,390; relative risk [RR] 1.2; 95% CI, 1.1–1.3). However, the overall risk of obesity was not greater between the highest versus lowest intake of artificial sweetened beverages (5 trials, N=22,390; RR 1.4; 95% CI, 0.96–2.0). The review was limited by moderate-to-high heterogeneity in subgroup analyses.

A 2020 systematic review and meta-analysis of 20 randomized controlled trials (RCTs; N=2,914) assessed the effects of non-nutritive sweeteners on body weight.[2] Patients in the RCTs were adults (16 trials, N=1,820) and children or adolescents (4 trials, N=1,094) who were either normal weight (4 trials, N=993) or overweight (14 trials, N=1,718); two trials (N=203) included normal and overweight individuals. Study duration ranged from 4 to 77 weeks (median 12.5 weeks). Non-nutritive sweeteners were aspartame, rebaudioside A, saccharin, stevia, and sucralose, while comparators were sucrose, water, or placebo/nothing. The primary outcome was the difference in mean body weight or BMI, expressed as the standardized mean difference (SMD) because of different weight measurement units. Overall, the consumption of non-nutritive sweeteners resulted in greater weight loss compared with sucrose (13 trials, N=1,997; SMD –0.56; 95% CI, –0.79 to –0.34), but not with water (4 trials, N=554; SMD –0.2; 95% CI, –0.62 to 0.23) or placebo/nothing (5 trials, N=363; SMD –0.06; 95% CI, –0.27 to 0.15). In a subgroup analysis of adult-only studies, non-nutritive sweeteners were more effective than any comparator in generating weight loss (16 trials, N=1,820; SMD –0.43; 95% CI, –0.64 to –0.22). Approximately half of all studies were at unclear or high risk of bias because of inadequate blinding of participants, personnel, or outcome assessors. Other limitations were the lack of information on trial location and funding sources for the individual RCTs.

A 2017 systematic review and meta-analysis identified seven RCTs (N=1,003) and seven prospective cohort studies (N=99,559) examining the association between non-nutritive sweeteners and obesity or weight change.[3] Eight trials were from the United States while Australia, Brazil, China, Denmark, Iran, and Spain each contributed one trial; five RCTs (N=788) and one cohort study (n=3,371) were also included in the above systematic reviews.[1,2] Patients had a mean age between 13 and 55 years old and a mean BMI between 20 and 37 kg/m^2. Study durations ranged from 6 to 24 months for the RCTs and 3 to 24 years for the cohort studies. Interventions in the RCTs included aspartame, stevioside capsules, or unspecified non-nutritive sweeteners in beverages and foodstuffs. Comparators included artificially sweetened beverage avoidance, water, and placebo. Cohort studies compared non-nutritive sweetener intake, almost entirely in the form of artificially sweetened beverages or sodas, either between lowest to highest intake quartiles or between no to any or daily intake. The primary outcome was change in BMI; secondary outcomes were change in body weight and incidence of overweight or obesity. For cohort studies where the non-nutritive sweetener intake units differed, the researchers calculated a mean correlation. In pooled analyses of the RCTs, intake of non-nutritive sweeteners did not cause a change in BMI (3 trials, N=242; mean difference [MD] −0.37 kg/m^2; 95% CI, −1.1 to 0.36) or a change in weight (5 trials, N=791; SMD −0.17 kg/m^2; 95% CI, −0.54 to 0.21) compared with avoidance, water, or placebo. However, cohort studies suggested non-nutritive sweetener intake was positively correlated with changes in BMI (2 trials, N=21,256; weighted mean correlation [WMC] 0.05; 95% CI, 0.03–0.06) and weight (4 trials, N=32,405; WMC 0.06; 95% CI, 0.05–0.07) and was associated with small increases in BMI (1 trial, n=3,371; MD 0.77 kg/m^2; 95% CI, 0.47–1.1) and incidence of overweight or obesity (3 trials, N=7,917 odds ratio 1.8; 95% CI, 1.3–2.7). The review was limited by unclear or high risk of bias in six of the seven RCTs. EBP

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Is there a relationship between socioeconomic status and quality of sleep in children and adolescents?

EVIDENCE-BASED ANSWER

Probably. A higher socioeconomic status is associated with increased sleep duration, better sleep quality, and early bedtime among children and adolescents (SOR: **C**, meta-analysis of cross-sectional studies and additional cross-sectional studies). The mechanisms driving this association are unclear.

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A 2020 meta-analysis of eight cross-sectional studies (N=72,477) evaluated the relationship between neighborhood socioeconomic status (nSES) and sleep duration.[1] Patients were medically and psychologically well children and adolescents 0 to 18 years old and 45.7% to 55.4% female. Both subjective and objective sleep duration was assessed. Subjective sleep duration was mostly measured by self-reported or parent-reported duration, whereas objective measures of sleep duration included actigraphy and cross-validated with a sleep diary. nSES exposure was defined variously across the studies such as percent of the population below the federal poverty level and socioeconomic index for areas. Overall sleep duration was significantly longer in higher nSES patients (8 studies, N=72,477; odd ratios [ORs] 1.26, 95% CI, 1.09–1.47). The effect of nSES on sleep duration was more pronounced with objective sleep assessment through actigraphy (2 studies, N=457; OR 2.09, 95% CI, 1.43–3.00) than with self-reported or parent-reported subjective sleep assessment (6 studies, N=72,020; OR 1.17, 95% CI, 1.03–1.32). This study was limited by heterogeneity in measures of nSES and sleep duration across the studies.

A 2014 cross-sectional study (n=239) examined socioeconomic gradients relative to sleep indices.[2] It could not be determined why this study was not included in the 2020 meta-analysis above. Patients were children 8 to 17 years old with a mean age of 12.6 years and 45.6% female. Exclusion criteria included use of medication with cardiovascular events or serious psychopathology. Sleep indices included sleep duration, daytime sleepiness, and sleep quality. Sleep duration was measured by youth or parent-reported bedtime and wake time on school nights for 1 month. Daytime sleepiness was scored on the pediatric daytime sleepiness scale by measuring the frequency of feeling sleepy during the day. Sleep quality was rated on a 10-point scale of feeling rested on awakening. Objective socioeconomic position (SEP) was defined as household income and parental education level. Subjective SEP was defined by the level selected by the youth on the subjective social status scale. Higher objective SEP was significantly related to longer self-reported sleep duration ($\beta=0.35$, $P<.01$). Higher subjective SEP was significantly related to less daytime sleepiness ($\beta= -0.33$, $P<.01$) and longer parent-reported sleep duration ($\beta=0.23$, $P<.05$). In addition, higher subjective SEP was significantly associated with better sleep quality ($\beta=0.28$, $P<.01$), but with shorter parent-reported sleep duration ($\beta= -0.18$, $P<.05$), even after controlling for objective SEP. This study was limited by lack of causation and additional variables not examined.

A 2013 cross-sectional study (n=1,845) examined the association between socioeconomic status (SES) and sleep patterns.[3] Similar to the 2014 study above, it could not be determined why this study was not included in the 2020 meta-analysis. Patients were children 5 to 10 years old with a mean age of 7.7 years and 52% female. Patients with lack of response to

questionnaire, missing data, or chronic medical problem affecting sleep were excluded. Sleep patterns were calculated using bedtimes, average wake time after sleep onset, and rise times on school nights and nonschool nights. For SES, patients were classified as low, mid, or high using the Australian Bureau of Statistics Socioeconomic Indexes for areas 2006 on household income, education, occupation, and ethnicity. Compared with those children with high SES, children from areas of low SES reported significantly later bedtimes both on school nights (low SES, 8:11 PM vs high SES, 8:05 PM, $P<.002$) and nonschool nights (low SES, 9:03 PM vs high SES, 8:46 PM, $P<.002$). There was a significant difference in mean sleep period time between low-SES and high-SES groups (low SES, 10 hours 39 minutes vs high SES, 10 hours 45 minutes, $P<.05$). It was unclear whether these statistically significant differences were clinically meaningful. The small response rate limited generalizability of results. In addition, subjective reports of sleep habits could be influenced by parents' social desirability bias or simple lack of knowledge. EBP

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Does goal-specific urate-lowering therapy improve outcomes versus a symptoms based approach in patients with tophus gout?

EVIDENCE-BASED ANSWER

Treat-to-target urate-lowering therapy (ULT) moderately reduces tophi burden in size and total number of tophi and also increases the velocity of size reduction of tophi (SOR: **B**, randomized controlled trials and cohort studies). When initiating ULT, the American College of Rheumatology strongly recommends a serum urate goal of <6 mg/dL (SOR: **C**, expert opinion).

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A 2018 parallel arm, nonblinded randomized controlled trial (RCT; n=517) assessed the efficacy of nurse-led care in treat-to-target (T2T) urate-lowering therapy versus usual care by general practitioners at achieving a serum urate (SU) level of <6 mg/dL (primary outcome) as well as differences in tophus burden (secondary outcome) over two years.[1] The population was primarily middle-aged White men, 20% of whom had tophi at baseline. Patients with severe or terminal illness were excluded. Initial treatment was with allopurinol (febuxostat, benzbromarone, or combination therapy were permitted based on patient's follow-up SU levels). Nursed-led T2T strategy led to more patients with a SU level <6 mg/dL (95% vs 30%; relative risk [RR] 3.2; 95% CI, 2.4–4.2), a reduction in percentage of patients with tophi (2.9% vs 11%; RR 0.21; 95% CI, 0.08–0.52, absolute risk reduction 8.4%; number needed to treat [NNT] =12), and a reduction in size of the largest tophi (3.3 vs

13 mm; mean difference 8.8; 95% CI, 3.8–13). The results of this RCT were limited by a lack of blinding as well as possible beneficial treatment effect from frequent nurse interventions (education, shared decision making, frequent follow-ups).

A 2013 RCT (n=212) examined the role of urate-lowering effect of pegloticase on overall tophus burden reduction during a 6-month interval, with 12-month follow-up extension, in patients with a history of chronic refractory gout who had failed to achieve a SU level <6 mg/dL after three months of allopurinol treatment.[2] Patients were enrolled from rheumatology clinics in the U.S., Canada, and Mexico with baseline SU >8.0 mg/dL. Exclusion criteria included severe illness, ongoing dialysis, pregnancy, and G6PD. Patients were randomized to receive 8 mg of pegloticase every two or four weeks or placebo. Patients in the biweekly group were more likely to achieve SU <6 mg/dL compared with the monthly group (42% vs 35%, placebo 8%; $P \leq .011$). Complete tophus resolution was also more likely in the biweekly group compared with the monthly group (45% vs 26%, placebo 8%; $P = .002$). Patients in the pegloticase groups did experience more adverse reactions than the placebo group (gout flares and infusion-related reactions were the most common adverse reactions). The clinical study was funded with pharmaceutical support.

The relationship between SU levels and the velocity of reduction of tophi was explored in a 2002 prospective cohort study (n=63).[3] Patients with chronic, tophaceous gout were enrolled in a long-term follow-up gout clinic and monitored until tophi resolution (mean 21 months, range 6–64 months). Patients were observed after treatment with allopurinol, benzbromarone, or a combination of the two in a dose-dependent fashion to achieve a SU level <7 mg/dL. The aim was to study the velocity of size reduction of tophi between groups. Lower serum uric acid levels were associated with a greater velocity of tophi size reduction (uric acids levels [mg/dL] 6.1–7.0, 5.1–6.0, 4.1–5.0, and <4.0 result in mean reduction velocity [mm/mo] of 0.53, 0.77, 0.99, and 1.5, respectively; linear correlation coefficient r=–0.62; $r^2 = 0.48$). During the trial, a trend towards more flares per patient was observed in groups with higher velocity reduction but this was not statistically significant. Treatment groups were assigned based on clinical characteristics, thus limiting interpretations of results since patients receiving combination therapy were likely to have larger urate stores at baseline than other groups.

Practice guidelines for the management of tophaceous gout were addressed by the 2020 American College of Rheumatology (ACR) Guidelines.[4] They recommended initiation of urate-lowering therapy in patients with subcutaneous tophi (strongly recommend, high certainty of evidence) and a T2T management strategy over a fixed-dose strategy (strongly recommend, moderate certainty of evidence). In addition, the ACR also recommended maintaining a SU target of <6 mg/dL over using no target (strongly recommend, high certainty of evidence). EBP

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Do proton pump inhibitors increase risk of recurrence in patients with frequent *C. difficile* colitis?

EVIDENCE-BASED ANSWER

Increased risk of recurrent *Clostridioides difficile* infection (CDI) is observed when taking gastric acid suppressants (SOR: **A**, meta-analysis of case–control studies, cohort studies, and clinical trials). Proton pump inhibitors (PPIs) exposure is an independent predictive factor for recurrent CDI (SOR: **B**, large case–control study). Use of PPIs before hospitalization for CDI, however, may not increase the risk of recurrent CDI (SOR: **C**, small cohort study).

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A 2017 meta-analysis of 16 case–control studies, cohort studies, and clinical trials evaluated the association of gastric acid suppressants and recurrent *Clostridioides difficile* infection (CDI; N=7,703).[1] Gastric acid suppressants included both proton pump inhibitors (PPIs) and histamine-2 blockers (H2B). Patients were from multiple countries including USA, Japan, Israel, and South Korea, and 52.4% used gastric acid suppressants. Among those patients using suppressants, the rate of recurrent CDI was 22.1% compared with 17.3% in patients not on suppressants (16 studies, N=7,703; odds ratio [OR] 1.52; 95% CI, 1.20–1.94; I^2=64%). Recurrent CDI was defined as symptoms recurring within 60 or 90 days of initial episode and associated with a positive stool test for C *difficile*. An increased risk of recurrent CDI for patients using gastric acid suppressants was noted in studies that defined recurrence within 90 days (7 studies, N=5,119; OR 1.53; 95% CI, 1.07–2.19; I^2=75%) and in studies that defined recurrence within 60 days (8 studies, N=2,533; OR 1.54; 95% CI, 1.04–2.28; I^2=61%). In addition, an increased risk of CDI recurrence was noted with PPIs (8 studies, N=5,409; OR 1.66; 95% CI, 1.18–2.34; I^2=75%) but not in studies that mentioned use of PPIs or H2Bs (8 studies, N=2,294; OR 1.37; 95% CI, 0.95–1.99; I^2=48%). The limitations included the heterogeneity of the studies' designs, populations, definitions of outcomes, tests used to diagnose CDI, reexposure to antibiotics, and use duration of gastric acid suppressants that led to the inability to control for all confounders such as demographics, number of prior CDIs, continuous versus intermittent acid medication use, duration and dose of medications, adherence to infection control practices, and the question of positive stool assays signifying colonization instead of infection.

A 2019 case–control study of both inpatient and outpatient U.S. Veterans Affairs (VA) patients examined factors for first recurrence of CDI in a national cohort of veterans (n=4,870).[2] Patients were veterans, 18 years old or older, with a first case of CDI treated at a VA facility between 2010 and 2014. First CDI case was defined using a positive stool sample for *C difficile* toxin by polymerase chain reaction and treatment with at least two days of oral or IV metronidazole, oral or rectal vancomycin, or fidaxomicin. First CDI recurrence was defined as a second episode of CDI occurring at least 14 days after the initial positive stool sample, as well as within 30 days posttreatment. Cases were paired with controls in a 1:4 ratio (974 cases to 3,896 controls). Controls were those veterans who did not develop a recurrence and were matched to cases based on year of initial episode of CDI, severity of CDI, and facility of treatment. PPI exposure was defined as use anywhere from 7 days before treatment up to 30 days after (number of days/doses not specified). PPI exposure was a significant independent predictive factor for CDI recurrence (OR 2.02; 95% CI, 1.59–2.55). Overall rate of recurrence within 30 days was 6.2%. Limitations included the possibility of over-the-counter PPI use that was not accounted for in study patients, and a high frequency of oral metronidazole use for treatment in patients, which was no longer the recommended standard of care per 2017 Infectious Diseases Society of America guidelines.

A small 2019 prospective longitudinal cohort study followed 75 patients through eight weeks posttreatment to assess clinical predictors of recurrent CDI.[3] Patients had mean age 58.1 years old, were 69.3% female, 74.7% White, and 54.7% using PPI therapy. Patients were admitted at three Boston area hospitals and experienced a primary episode of uncomplicated CDI with no CDI infections in the preceding six months. Exclusion criteria were inflammatory bowel disease, inherited or acquired immunodeficiency, fulminant CDI, and non-CDI antibiotic therapy extending past the CDI antibiotic course. Stool was collected at least weekly through the 8 weeks and sent for *C difficile* testing if patients were experiencing more than two

bowel movements a day (Bristol stool scale 6 or 7) for three days. Prior PPI use did not increase risk of recurrence. Of the 41 patients with prior PPI use, 10 patients (45.5%) did have recurrent CDI and 31 patients (58.5%) did not have recurrent CDI ($P=.301$). Primary CDI infection treatment with metronidazole and primary diagnosis with the glutamate dehydrogenase antigen were the most significant predictors of recurrent CDI. Limitations were the focus on patients with uncomplicated CDI, the exclusion of patients who were immunocompromised because of medications or disease, the treatment of 22.7% of patients with metronidazole that was no longer the treatment of choice, and the focus on patients with prior use of PPI without study of PPI use after their first CDI illness. EBP

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What is the best treatment of opioid withdrawal in newborn infants?

EVIDENCE-BASED ANSWER

For neonatal opioid withdrawal syndrome (NOWS) treatment, sublingual buprenorphine, diluted tincture of opium, and clonidine are all superior to morphine, reducing hospital stay by about a week (SOR: **B**, systematic review, low-quality randomized controlled trials [RCTs]). Opiate class medications may be more successful than benzodiazepines for treating symptoms (SOR: **B**, systematic review, low-quality RCTs). Experts recommend treating NOWS with nonpharmacologic measures, followed by pharmacologic therapy, preferably opioids, for persistent symptoms despite nonpharmacologic interventions (SOR: **C**, practice guideline).

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A 2021 systemic review of 16 randomized controlled trials (RCTs; N=1,110) assessed the effectiveness and safety of using an opioid for treating neonatal abstinence syndrome (NAS) in newborn infants withdrawing from opioids.[1] Patients were mostly term or near-term infants with NAS symptoms born to mothers with opioid dependence. Most trials used a validated system (eg, Finnegan or Lipsitz score) to identify neonates with NAS symptoms, and most used a scoring system to titrate pharmacologic treatment. Opioid interventions were morphine, methadone, and camphorated tincture of opium (paregoric). When reported, daily morphine doses ranged from 0.05 to 0.9 mg/kg/d. Comparators were supportive care only, another opioid (methadone, sublingual buprenorphine, or diluted tincture of opium) or a sedative medication (clonidine, diazepam, phenobarbital, or chlorpromazine). Most studies used oral administration to deliver the medication. The primary outcome was treatment failure, defined as the need to add a second pharmacologic agent or failure of an agent to reduce the NAS score of from a clinically significant level to a clinically "safe" level, as defined by the authors of the individual studies. Secondary outcomes included time to regain birthweight and length of hospital stay. Morphine as an adjunct to supportive care was not superior to supportive care alone or to treatment with another opioid for reducing the risk of treatment failure, but morphine and other opioids were more successful than sedative

TABLE. Opioid treatment for opioid withdrawal in neonates

Intervention vs control	No. of trials	No. of infants	Relative risk of treatment failure (95% CI)[a]	Average difference in length of stay in days (95% CI)[b]
Morphine vs supportive care[c]	1	80	1.3 (0.41–4.1)	15 (8.9–21.1)
Morphine vs methadone	2	147	1.6 (0.95–2.7)	NA[d]
	1	116	NA	1.4 (–3.1 to 5.9)
Morphine vs sublingual buprenorphine	3	113	0.79 (0.36–1.7)	11.4 (5.9–17)
Morphine vs diluted Tincture of Opium	1	33	NA	5.1 (2.1–12.3)
Morphine vs clonidine	1	31	NA	6.1 (0.78–13)
Opioid vs diazepam	2	86	0.43 (0.23–0.8)	NA
Opioid vs phenobarbital	6	452	0.59 (0.41–0.86)	NA
Morphine vs chlorpromazine	1	96	0.05 (0.01–0.36)	NA

Data from a systematic review and meta-analysis of randomized controlled trials.[1] [a] Treatment failure was defined as the need to add a second pharmacologic agent or failure of an agent to reduce a standardized neonatal abstinence syndrome score from a clinically significant level to a clinically "safe" level. [b] The difference in length of stay was defined as the intervention group hospital stay minus control group hospital stay, measured in days. [c] Supportive care included using a pacifier, swaddling, close wrapping, frequent small feedings, carrying in sling to promote close skin contact, warm bathing, and other methods as needed to help calm the newborn. [d] NA=data not available.

medications (diazepam, phenobarbital, and chlorpromazine) (**TABLE**). Newborns given morphine required fewer days to regain birth weight compared with those who received supportive care only (1 trial, n=80; mean difference –2.8 days; 95% CI, –5.3 to –0.27 days). Morphine increased hospital stay compared with supportive care or another opioid but not when compared with clonidine. When compared with diazepam, phenobarbital, and chlorpromazine, opioid treatment had no significant effect on the length of hospital stay (**TABLE**). The review was limited by low- to very low- quality evidence mainly because of small sample sizes in most of the RCTs as well as unclear risk of bias from selective reporting in 10 of the trials. The trials did not report or were underpowered to detect differences in treatment-related adverse events such as seizures and infant mortality.

A 2020 clinical report from the American Academy of Pediatrics on neonatal opioid withdrawal syndrome (NOWS) recommended that initial treatment include nonpharmacologic measures including identifying NOWS triggers and employing comfort measures to prevent or control NOWS symptoms (no strength of recommendation or level of evidence provided).[2] For neonates with severe NOWS, the report recommended that pharmacologic therapy, preferably an opioid, be considered if symptoms persisted despite nonpharmacologic interventions to improve withdrawal symptoms and minimize complications. The report stated that clonidine or phenobarbital could be used (usually in addition to an opioid) for persistent NOWS symptoms with the caveat that clonidine was preferred because of concern for possible adverse neurodevelopmental outcomes with phenobarbital therapy. The report recommended against camphorated tincture of opium (paregoric) and other products containing high amounts of ethanol. The report was based on a narrative literature review, without an explicit description of the methodology or criteria used to select articles. EBP

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In adult females with symptoms of an uncomplicated urinary tract infection, does treatment by virtual visit improve patient-oriented outcomes compared with standard treatment?

EVIDENCE-BASED ANSWER

The evidence is slim that any difference exist. Patients treated virtually for their uncomplicated urinary tract infection (UTI) may be less likely to need an unplanned visit one week after treatment compared with those seen in the office (SOR: **B**, cohort studies with different findings). Antibiotic prescribing rates, UTI complication rates, and the need to adjust antibiotic treatment are likely not altered with virtual treatment (SOR: **B**, cohort study).

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A 2020 retrospective cohort study (n=325) compared antimicrobial prescribing practices between virtual visits and office visits for adults diagnosed with uncomplicated urinary tract infections (UTIs) within a primary care network.[1] Patients were females (18–65 years old) diagnosed with an uncomplicated UTI during a virtual or office visit occurring over 12 months. Patients with virtual visits (n=175) completed an asynchronous symptom and history questionnaire through the Zipnosis® platform. A provider confirmed the diagnosis of uncomplicated UTI and selected a treatment plan from preset antibiotic and supportive care options (including dose and duration) based on national guidelines. Patients assessed in the office (n=175) completed a typical office visit without requiring the provider to use a standard UTI template. The primary outcome measured was guideline concordance, based on the Infectious Diseases Society of America treatment guidelines. Patients treated by virtual visits were more likely to receive a first-line antibiotic (74.9% vs 59.4%; $P=.002$) and guideline-concordant treatment duration (100% vs 53.1%; $P<.001$). Patient-oriented secondary outcomes included unplanned revisits within 48 hours, seven days, and 30 days. Revisits included office, urgent care, emergency department, or virtual visits for unresolved UTI symptoms. Revisit frequency was similar in the two groups at 48 hours (10.3% vs 11.4%; $P=.73$) and 30 days (26.9% vs 24.0%; $P=.54$), but were more frequent within seven days for those with an office visit (relative risk=0.27; 95% CI, 0.14-0.55). In multivariate logistic regression analysis, the only factor independently associated with an unplanned revisit within seven days was initial care through an office visit (odds ratio=3.74; 95% CI, 1.31–10.67). Limitations included incomplete chart data and a selection bias toward older patients in the office visit group (median age 37 vs 46 years old; $P<.001$).

A 2019 retrospective cohort study (n=450) compared the antibiotic prescribing, clinical outcomes, and follow-up rates for the online assessment and treatment of symptoms of uncomplicated UTI by face-to-face visits and nurse phone protocols.[2] The study reviewed encounters for adult females (18-65 years old) who had a face-to-face visit at a retail acute care clinic (n=150), a nurse phone protocol encounter (n=150), or an eVisit® for urinary symptoms (n=150). Patients with recent evaluation for urinary complaints, recent urinary procedure, pregnancy, or risk factors for complicated UTI were excluded. Primary outcomes included the rate of oral antibiotic treatment, incidence of clinical outcomes (treatment extension or adjustment,

pyelonephritis diagnosis, and sepsis or hospitalization), and 30-day follow-up rates. Patients evaluated by eVisit completed a symptom-specific question set asynchronously on a secure online patient portal. An advanced practice provider (APP) responded to the inquiry within an hour. The face-to-face group was evaluated by APPs on a walk-in basis. No difference in antibiotic treatment rates was noted between eVisits and face-to-face encounters (81% vs 83%, $P=.90$). Patients who had an initial eVisit were significantly more likely to be advised to have follow-up compared with patients evaluated by a face-to-face visit (RR 2.2; 95% CI, 1.2–4.1) but were not more likely to seek follow-up care (32% for eVisit vs 26% for face-to-face, $P=.46$). No significant difference in clinical outcomes was noted between the initial encounter types. This study was limited in its retrospective nature and potential selection bias in those patients willing to seek care through each option. EBP

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Is elagolix safe and effective in the treatment of endometriosis pain?

EVIDENCE-BASED ANSWER

Yes, elagolix (150 mg daily or 200 mg twice daily) decreases moderate-to-severe endometriosis pain including dysmenorrhea and nonmenstrual pelvic pain (SOR: **A**, multiple randomized controlled trials [RCTs]). Adverse events are more common after 12 months of elagolix treatment than six months. Lumbar spine bone mineral density decreases by up to 4% for patients receiving 200 mg twice daily for 12 months (SOR: **A**, multiple RCTs).

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A 2020 nonsystematic review pooled data of two phase III RCTs (N=1,686) that compared the efficacy and safety of elagolix with placebo in premenopausal women for the treatment of endometriosis.[1] Patients were 18 to 49 years old, who had received a surgical diagnosis of endometriosis in the previous 10 years and had moderate-to-severe endometriosis-associated pain. Trial patients were given elagolix 150 mg by mouth daily (n=475), elagolix 200 mg by mouth twice daily (n=477), or placebo (n=734) for six months with a 12-month follow-up period. The primary outcome was measured using the Endometriosis Health Profile–30 (EHP-30) questionnaire at baseline and one, three, and six months of treatment. The EHP-30 assesses five health-related quality of life domains, including pain with a range of 0 to 100, with lower scores indicating better health-related quality of life. The outcomes included nonmenstrual pelvic pain at three months of treatment and a clinical response for dysmenorrhea. Compared with placebo, the elagolix 150 mg daily group reported statistically and clinically significant improvement in pelvic pain at one month (2 trials, N=1,209; least squares mean difference [LSMD] –5.3; 95% CI, –7.4 to –3.1), three months (2 trials, N=1,209; LSMD –8.3; 95% CI, –10.7 to –5.9), and six months (2 trials, N=1,209; LSMD –10.7; 95% CI, –13.5 to –7.9). The elagolix 200 mg twice daily group (vs placebo) reported a higher magnitude of clinical improvement than the elagolix 150 mg group in pelvic pain at one month (2 trials, N=1,211; LSMD –8.7, 95% CI, –10.9 to –6.5), three months (2 trials, N=1,211; LSMD –17.1; 95% CI, –19.5 to –14.7), and six months (2 trials, N=1,211; LSMD –21.1; 95% CI, –24.0 to –18.2). Limitations included recall bias and lack of applicability to women with milder endometriosis.

Two 2018 phase III extension RCTs (N=569) evaluated an additional six months of efficacy and safety of elagolix in women with moderate-to-severe endometriosis-associated pain.[2] Patients were premenopausal women, with the median age of 31 and 34 years old, with a surgical diagnosis of endometriosis who had completed the 6-month treatment period in either of the preceding trials. Patients received the same elagolix dose as previously taken, either 150 mg daily (n=291) or 200 mg twice daily (n=278), for an additional six months with a posttreatment follow-up period of up to 12 months. The primary outcomes included the proportion of responders for dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia based on self-reported daily pain assessments and rescue analgesic use. The original trails showed a clinically meaningful reduction from baseline in dysmenorrhea at 150 mg daily (52% and 51%) and at 200 mg twice daily (78% and 76%). Similar clinically meaningful decreases were observed during the extension period for 150 mg daily (68% and 66%) and 200 mg twice daily (69% and 67%). At least one adverse event was experienced by approximately 90% of women treated over 12 months with elagolix. Common adverse events included hot flush, headache, and nausea and were more often observed at the 200 mg twice daily dose. In addition, lumbar spine bone mineral density decreased from baseline by –0.63% and –1.1% for the 150 mg daily group and –3.6% and –3.9% for the 200 mg twice daily group after 12 months of treatment.

A 2013 RCT (n=137) evaluated the efficacy of elagolix on the treatment of endometriosis-associated pain.[3] Patients were women, with a median age of 33 years old, predominately being White (81.7%), and moderate-to-severe nonmenstrual pelvic pain and dysmenorrhea and laparoscopically confirmed endometriosis. The study entailed an 8-week screening period and an 8-week double-blind intervention period, followed by 16-week open-label and 6-week follow-up periods. Patients were randomized to 150 mg elagolix daily (n=68) or placebo

(n=69) for eight weeks. At the end of eight weeks, all active patients received open-label elagolix 150 mg daily for 16 more weeks. A modified Biberoglu–Behrman pain scale was used for daily assessment of dysmenorrhea and nonmenstrual pain on a 4-point scale (0=no pain to 3=severe pain). Compared with the placebo group, both clinically and statistically significantly greater pain reduction in dysmenorrhea pain (–1.1 vs –0.4, $P<.0001$) and nonmenstrual pelvic pain (–0.5 vs –0.2, $P=.0066$) was observed in the elagolix 150 mg group after eight weeks of treatment. At the end of the open-label period, no significant pain score reduction was observed for dysmenorrhea or nonmenstrual pain in both groups. Approximately 50% of the elagolix and placebo patients experienced any adverse event during the 8-week double-blind period; 70% of the elagolix patients experienced adverse events through the 24-week treatment period, with 12% serious events. The most commonly occurring adverse events were headache, hot flush, and nausea. No deaths occurred. Limitations included a short double-blind treatment period, high dropout rate due to maintenance of pain on placebo, and inclusion of patients who were not elagolix-naïve. EBP

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