July 2021

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

July 2021
Volume 24 | Number 7

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Family Physicians Inquiries Network

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

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

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STATEMENT OF PURPOSE

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

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DISCLOSURE

The PURLs Surveillance System is supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

Do shared medical appointments for adults with diabetes mellitus type 2 and obesity increase weight loss versus traditional appointments?

EVIDENCE-BASED ANSWER

Shared medical appointments compared to traditional appointments are associated with small amounts of additional weight loss for overweight or obese patients with diabetes mellitus type 2, but inconsistent results for changes in body mass index (SOR: **B,** 2 randomized control trials and a case series).

DOI 10.1097/EBP.0000000000001109

A 2004 five-year randomized control trial (RCT) (N=112) analyzed the effects of shared medical appointments (SMAs) for patients with diabetes mellitus type 2 (DM-2) on quality of life, knowledge of diabetes, and problem-solving ability.[1] All patients had DM-2, were not on insulin, and had been part of a hospital-based diabetes office in Italy for more than one year. Most patients were obese or overweight at baseline (intervention group mean weight 80 kg and body mass index (BMI) 30 kg/m^2; control group mean weight 78 kg and BMI 28 kg/m^2). Patients were 48% to 60% male with an average age 61 to 62 years old (range 35–80 years old). The control group had traditional 15-minute individual appointments every three months. The intervention group participated in SMAs every three months with a set curriculum consisting of brief, individual visits and group support education including presentation, interactive learning, peer experience sharing, and homework for the next session. SMA groups contained 9 to 10 people and were led by one to two physicians and an educationist. Body weight decreased significantly in SMA participants (–3.5 vs –0.24 kg; $P<.015$). There was no difference in BMI between SMA and control groups (–1.4 vs –0.1 kg/m^2; $P=.067$). There was a lack of blinding of SMA patients and facilitators. There were 14 dropouts from each group, most due to a change in clinic.

In 2010, a RCT (N=815) by the same research group looked at reproducibility of SMA in diabetic patients at multiple clinics.[2] Diabetic patients were non-insulin users, age <80 years old, overweight or obese (78–81 kg, BMI 29–31 kg/m^2) from hospital-based diabetes clinics and randomized to either SMA (model described above) or to traditional one-to-one visits. Outcomes included BMI and body weight. At four years, the SMA group had greater reductions in body weight and BMI compared to traditional office visit group (mean difference [MD] –3.5 kg, 95% CI, –4.2 to –2.1 kg and MD –1.1 kg/m^2; 95% CI, –1.6 to –0.62 kg/m^2). Two clinics dropped out of the study.

A 2016 case series compared the impact of a culturally tailored SMA to a traditional office visit for adult diabetic patients self-identified as Black Americans (N=250).[3] Mean patient age was 57 years old and all patients had HbA1c >7.0% with or without the use of insulin. Patients in the SMA and traditional office visit groups included 65 and 53% female, baseline HbA1c 9.4 and 8.7%, and BMI 35 and 36 kg/m^2. SMA sessions of 9 to 20 adults included an individual diabetic exam, a group interactive session facilitated by the physician and a nurse practitioner discussing diabetic complications, risks, clinical measure goals and medication overview, and group counseling on glucose monitoring, and lifestyle (nutrition, food label comprehension, cultural food exchanges and fitness). There was no difference in BMI between the SMA group and the traditional appointments group (35.02–34.98 kg/m^2 and 36.141–36.149 kg/m^2; between group t test=.17, $P=.87$). Patients that only participated in one SMA session were included. This small population in a limited demographic may not be reproducible on a large scale. EBP

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The authors declare no conflicts of interest.

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Oral paracetamol versus combination oral analgesics for acute musculoskeletal pain

Gong J, Colligan M, Kirkpatrick C, Jones P. Oral paracetamol versus combination oral analgesics for acute musculoskeletal injuries. *Ann Emerg Med*. 2019; 74(4): 521–529.

DOI 10.1097/EBP.0000000000001173

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

This prospective, double-blind, randomized, controlled, parallel-arm study performed at an urban tertiary hospital emergency department compared a combination of oral paracetamol, ibuprofen, and codeine with paracetamol alone for pain relief in 119 patients. Patients were 18 to 65 years old with acute (<48 hours) closed limb or trunk injuries with moderate pain (>3 on a 10-point pain scale). A single dose of paracetamol 1 g, ibuprofen 400 mg, and codeine 60 mg was compared with a single dose of paracetamol 1 g, placebo ibuprofen, and placebo codeine. The primary outcomes were change in baseline pain at rest and activity with follow-up measurements at 60 and 120 minutes. Secondary outcomes included side effects and need for rescue analgesia. A difference of 1.3 on the 10-point pain scale was set as the minimum clinically detectable value. At 60 minutes, no difference was observed between the groups for pain reduction at rest (mean difference (MD), –0.4 (95% CI, –1.1 to 0.29) or activity (MD, –0.2; 95% CI, –0.9 to 0.5). At 120 minutes, no difference was observed in pain reduction at rest (MD, –0.5; 95% CI, –1.6 to 0.5), but on activity, there was significantly less pain in the combination group but it did not reach clinical significance (MD, –1.1; 95% CI, –2.3 to 0.1). The dropout rate at 120 minutes was 37% in the combination group and 49% in the paracetamol group. At 60 minutes, no difference was observed between groups in the need for rescue analgesia (risk ratio [RR], 1.2; 95% CI, 0.35–4.4). There were more adverse events in the combination group compared with the paracetamol group (14 vs 5; RR, 2.8; 95% CI, 1.1–7.2; number needed to harm=7). Study limitations include more fractures in the paracetamol group and a high dropout rate before the 120-minute pain score. Codeine has a peak effect at up to 60 to 90 minutes, so it may not have had full effect by 60 minutes. Nonpharmacologic treatments, such as ice, compression, elevation, and splints, were not recorded. In summary, the combination of oral paracetamol, ibuprofen, and codeine for moderate to severe pain associated with acute musculoskeletal injuries was not superior to paracetamol alone.

Bottom line: The practice of combining oral paracetamol, ibuprofen, and codeine as the initial treatment for moderate to severe pain associated with acute MSK injuries as compared with paracetamol alone is not supported by this study.

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The author declares no conflicts of interest.

Choice is yours but don't be late: lung cancer screening may prevent lung cancer–related death

Agency for Healthcare Research and Quality. Evaluation of the benefits and harms of lung cancer screening with low-dose computed tomography: a collaborative modeling study for the US Preventive Services Task Force. 2020; AHRQ Publication No. 20-05266-EF-2. https://www.uspreventiveservicestaskforce.org/uspstf/document/draft-decision-analysis/lung-cancer-screening-2020.

DOI 10.1097/EBP.0000000000001190

This Clinic Practice Guideline is an update to a 2014 clinical practice guideline. The US Preventive Services Task Force (USPSTF) used two methods to provide the best possible evidence for the recommendations. First, they performed a systematic review of the accuracy of screening for lung cancer with low-dose computed tomography (CT) scan, evaluating

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

both the benefits and harms of lung cancer screening, as well as various approaches to reduce false-positive results. Second, the USPSTF used collaborative modeling studies to provide the following information: the optimum age for beginning and ending screening; the optimal screening interval and the relative benefits and harms of different screening strategies.

Seven randomized controlled trials (RCT), plus the modeling studies, were evaluated. Only the National Lung Cancer Screening Trial (NLST; N=53,454) and the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON; N=15,792) trials had adequate power to detect a mortality benefit from screening. The NLST reported a relative risk of 16% (95% CI, 5–25), whereas the NELSON found an incidence rate ratio of 0.75 (95% CI, 0.61–0.90).

Screening intervals, from the NLST and NELSON trials, as well as from the modeling studies showed greatest benefit from biennial screening (statistics not given). Evidence also found that screening those with lighter smoking histories and at an earlier age provided increased mortality benefit (<30 pack-years and age 50 years, respectively). No evidence was found for benefit of screening past 80 years old. The modeling studies found that the 2014 USPSTF screening program, using a starting age of 55 years and a 30-pack-year smoking, would reduce mortality by 9.8%. Changing to a starting age of 50 years, a 20-pack-year smoking history and annual screening would reduce mortality by 12.1–14.1%. There was insufficient evidence to show that prediction model-based screening offered any benefit beyond that of the age and smoking history risk factor model.[1]

The incidence of false-positive results was >25% in the NLST at baseline and at one year. Use of a classification system like Lung-reporting and data system could reduce that from 26.6% (95% CI, 26.1–27.1%) to 12.8% (95% CI, 12.4–13.2%).[2] Evidence from several RCT and cohort studies showed the exposure from one low-dose computed tomography (LDCT) scan to be 0.65 to 2.36 mSv, whereas the annual background radiation in the United States is 2.4 mSv. The modeling studies estimated that there would be one death caused by LDCT for every 18.5 cancer deaths avoided.

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, USPSTF, and PubMed with the terms screening, low-dose CT, and lung cancer, to find additional literature to place this research into the context of current clinical practice.

Bottom line: Annual low-dose CT scanning to screen for lung cancer has a USPSTF B recommendation (moderate certainty of moderate net benefit) based on age (50 years old), total cumulative exposure to tobacco smoke (20 pack-years), and years (15) since quitting smoking. This benefit does not extend beyond 80 years old or where other conditions make life-expectancy short.

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The authors declare no conflicts of interest.
The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

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CRP for CAP, a new diagnostic approach?

Ebell MH, Bentivegna M, Cai X, Hulme C, Kearney M. Accuracy of Biomarkers for the Diagnosis of Adult Community-acquired Pneumonia: A Meta-analysis. *Acad Emerg Med*. 2020; 27(3):195-206. doi:10.1111/acem.13889.

DOI 10.1097/EBP.0000000000001209

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

This meta-analysis of cohort studies evaluated the utility of biomarkers, including rapid C-reactive protein (CRP) and procalcitonin (PCT), for diagnosing community-acquired pneumonia. Studies were included if they collected data in patients presenting with acute respiratory tract infection or clinically suspected pneumonia and reported sufficient information to calculate sensitivity and specificity for at least one biomarker. Data collection could be prospective or retrospective, but studies needed to obtain biomarker and chest x-rays on all patients. Bivariate meta-analysis was performed to create summary receiver operating characteristic (ROC) curves for each biomarker.

A total of 829 studies were reviewed in parallel by two reviewers; all studies were reviewed by the lead author and 14 were included in the meta-analysis. All but two studies (1 from the United States and 1 from Chile) were from Europe. About half of enrolled patients were from emergency rooms, whereas the other half were from primary care offices. Based on QUADAS2-2 criteria, eight of the studies were judged to have a low risk of bias and six moderate risk of bias; mostly, this was because of uncertain blinding of radiologists. Sufficient data were accumulated to create ROC curves for C-reactive protein (CRP), procalcitonin, and white blood cell count. Based on areas under the ROC curves, CRP was the most accurate of all biomarkers. The cutoff chosen could determine whether CRP would rule out CAP (CRP $<$10 or 20 mg/L) or rule in CAP (CRP$>$50 or 100 mg/L). Using a cutoff of $>$50 mg/L to rule in CAP would produce a positive likelihood ratio of 3.68 and a negative likelihood ratio of 0.36. Authors further concluded that given cost and availability considerations, CRP could be useful at the point of care to determine whether to order imaging or prescribe antibiotics for patients presenting with lower respiratory symptoms.

Methods

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

Bottom Line: Although readily available in hospital emergency rooms and in outpatient offices in Europe, CRP has not been approved by the FDA as a point of care test for primary care offices in the United States. Until this barrier is removed, using CRP as a decision tool for ordering imaging or prescribing antibiotics will be problematic for many primary care providers in the United States. Also, CRP is now being used in conjunction with other laboratory data to determine severity and prognosis for patients hospitalized for the treatment of moderate-to-severe SARS-CoV-2.

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Your water is not basic enough: dietary changes can improve symptoms of LPR

A comparison of alkaline water and mediterranean diet versus proton pump inhibition for treatment of laryngopharyngeal reflux

Zalvan CH, Hu S, Greenberg B, Geliebter J. A comparison of alkaline water and mediterranean diet vs proton pump inhibition for treatment of laryngopharyngeal reflux. *JAMA Otolaryngology Head Neck Surg*. 2017; 143(10):1023–1029.
DOI 10.1097/EBP.0000000000001145

KEY TAKEAWAY: Changes in lifestyle, including eating a Mediterranean diet and drinking alkaline water, can improve laryngopharyngeal (LPR) symptoms just as effectively as proton pump inhibitors (PPIs).

STUDY DESIGN: Retrospective cohort study.

LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFO: LPR is a common missed diagnosis associated with a myriad of symptoms, including chronic cough. PPIs are often used as treatment, but these medications come with cost and side effects.

PATIENTS: Patients diagnosed with LPR in senior author's clinic in Sleepy Hollow, NY.
INTERVENTION: Alkaline water (pH>8.0), plant-based, Mediterranean-style diet, and standard reflux precautions for six weeks.
CONTROL: PPI with standard reflux diet and precautions for six weeks.
OUTCOME: Change in reflux symptom index (RSI) by at least six points.

METHODS BRIEF DESCRIPTION: Patient medical records from a single clinic were retrospectively reviewed and identified those patients diagnosed with LPR in a five-year period. Participants were excluded if they had prior vocal cord disorders, esophageal disorders, neuropathic cough, currently smoked, or had chronic allergies or sinusitis. Two cohorts were identified: those treated with PPI (either esomeprazole twice daily or dexlansoprazole daily) and those treated with dietary changes over a six-week period. Dietary changes included eating mostly produce, whole grains, and nuts, while limiting animal-based products, as well as replacing all beverages with water with pH greater than 8.0 (alkaline). Treatment response was measured using the RSI.

INTERVENTION (# IN THE GROUP): 99.
COMPARISON (# IN THE GROUP): 85.

FOLLOW-UP PERIOD: Six weeks.

RESULTS:
Primary outcome: ≥six-point reduction in RSI
- The RSI scores nine questions related to reflux symptoms and grades them on a scale of 0 to 5 (5 being severely problematic for the patient). A score of greater than 13 is considered indicative of LPR.
- No statistical difference between mean reductions in PPI cohort and AMS cohort. 54.1% of controls and 62.6% of intervention patients (difference, 8.5%; 95% CIs, –5.74 to 22.76).

Additional outcome measured after results calculated above:
- Mean reduction in RSI was 27.2% in PPI treated versus 39.8% in the AMS group (difference, 12.6%; 95% CI, 1.53–22.68).
- Statistically significant difference in percent reduction between these groups in favor of AMS cohort.

LIMITATIONS:
- Retrospective study design.
- Diagnosis of LPR was not objectively confirmed.
- It is unclear if patients from the first cohort were included in the second cohort.
- The study may have falsely positive results if patients lost weight during study interval and may have falsely negative results if they had concurrent diseases which mimic LPR.
- PPI use was not evaluated.
- The study was not powered to measure subgroup responses. EBP

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The author declares no conflicts of interest.

Hocus pocus or POCUS: Ultrasound for diagnosing pneumonia in children

Lung ultrasound in the diagnosis of pneumonia in children with acute bronchiolitis

Biagi, Carlotta; Pierantoni, Luca, et al. Lung ultrasound in the diagnosis of pneumonia in children with acute bronchiolitis. *BMC Pulm Med*. 2018; 18(1):191.
DOI 10.1097/EBP.0000000000001170

KEY TAKEAWAY: Lung ultrasound (LUS) has favorable sensitivity and specificity in diagnosing bacterial pneumonia in children hospitalized with bronchiolitis.

STUDY DESIGN: Prospective diagnostic study.

LEVEL OF EVIDENCE: STEP 3

BACKGROUND: Bronchiolitis is a common lower respiratory tract infection and is a leading cause of hospitalization in children under two years old. Although the American Academy of Pediatrics recommends reserving chest X-ray for severe cases, it is frequently obtained during evaluation of respiratory illnesses. Point-of-care LUS is an emerging diagnostic tool performed at the bedside by the clinician that has shown good sensitivity and specificity for pneumonia.

PATIENTS: Children <24 months of age with bronchiolitis.
INTERVENTION: Point-of-care LUS.
CONTROL (COMPARISON): Chest X-ray.
OUTCOME: Pneumonia.

METHODS BRIEF DESCRIPTION:
- This prospective diagnostic study was performed in a pediatric emergency unit in Bologna, Italy.
- The study enrolled children 0 to two years old admitted to the hospital from February 2016 to April 2017 with bronchiolitis (per American Academy of Pediatrics Guidelines). Children with chronic lung disease and congenital or acquired immunodeficiency were excluded. All participants had a posteroanterior chest X-ray.
- Within 12 hours, study participants underwent a bedside ultrasound. LUS was performed by a pediatrician who had attended an eight-hour LUS training session with supervised practical training. The criteria to define pneumonia by LUS was the finding of a hypoechogenic area with poorly defined borders that interacted with the pleural line and was associated with B lines, air bronchograms, and reduced or absent lung sliding.
- Chest X-rays were interpreted by a radiologist who was blinded to clinical and laboratory data. Bacterial pneumonia was defined as a chest X-ray with "consolidation," "infiltrate," or "pneumonia" by the radiologist. Viral infections were defined as a reading of "likely viral infiltrates," "peri-bronchial thickening," "peri-bronchial cuffing," or "increased interstitial markings."
- The diagnostic gold standard for the study was the diagnosis of bacterial pneumonia made by an experienced pediatrician blinded to the LUS findings, based on clinical presentation, laboratory tests, chest X-ray and clinical course following the British Thoracic Society Guidelines recommendations.

INTERVENTION (# IN THE GROUP): 87.
COMPARISON (# IN THE GROUP): N/A.

FOLLOW-UP PERIOD: February 2016 to April 2017.

RESULTS:
- There was strong agreement between chest X-ray and LUS in diagnosing bacterial pneumonia which improved with consolidation >1 cm:
- Chest X-ray showed a sensitivity of 96% (95% CI, 88.8–98.8%) and specificity 87.1% (95% CI, 77.8–93.0%) in identifying concomitant pneumonia in children diagnosed with bronchiolitis.
- LUS showed a sensitivity of 100% (95% CI, 94.7–99.9%) and a specificity of 83.9% (95% CI, 74.1–90.6%).
- When ultrasound consolidation size greater than 1 cm was considered consistent with pneumonia, LUS sensitivity was 80.0% (CI, 69.8–87.5%) and specificity was 98.4% (95% CI, 92.2–99.8%).

LIMITATIONS:
- This was a single-center study.
- There was a high prevalence of disease (29%) of patients diagnosed with secondary bacterial pneumonia. This suggests a skewed study population as only hospitalized children were evaluated where the pretest clinical suspicion of pneumonia was high.

- The only true "gold standard" for identifying pneumonia is chest computed tomography; this was not ethically possible; therefore, a clinician examiner was used. Diagnostic guidelines were used but are still subject to the bias/opinion of the examiner. The study also did not indicate how many examiners were used.
- The radiologists in the study diagnosed pneumonia without a set standard for their impression.
- A single view of the chest was obtained to minimize radiation exposure. It is debated in the literature if single view chest X-ray is sufficient for radiographically diagnosing pneumonia.
- The article did not state how many radiologists or sonographers were in the study.

EBP

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The author declares no conflicts of interest.

What interventions are effective for preventing injurious falls in older adults?

EVIDENCE-BASED ANSWER

Exercise alone reduces the risk of injurious falls by about 50% for all older adults when compared with usual care (SOR: **A**, systematic review and meta-analysis of randomized controlled trials). Exercise when combined with other interventions (eg, vision assessment and treatment, environmental assessment and modification, combined clinic-level quality improvement strategies, multifactorial assessment, and vitamin D and calcium supplementation) may further reduce the risk of injurious falls by 70% to 88% (SOR: **A**, systematic review and meta-analysis). For community-dwelling older adults, exercise alone reduces the rate of injurious falls by about 20% (SOR: **A**, systemic review). In addition to exercise, the U.S. Preventive Services Task Force (USPSTF) recommends clinicians to selectively offer multifactorial interventions for these adults but recommends against vitamin D supplementation to prevent falls in community-dwelling adults 65 years old and older (SOR: **B**, USPSTF recommendations **B**, **C**, and **D**, respectively).

DOI 10.1097/EBP.0000000000000820

A 2017 systematic review and network meta-analysis found 283 randomized controlled trials (RCTs) (N=159,910) comparing the effectiveness of 39 various interventions versus usual care for preventing falls in people 65 years old and older.[1] Of these studies, 54 RCTs (N=41,596) specifically evaluated for the primary outcome of injurious falls. The majority of the studies were multicenter parallel RCTs in Europe. The mean age of study participants was 78.1 years, and 73% were female. A majority of the interventions were studied in community-dwelling populations, whereas 24% were in retirement homes or long-term care facilities. Half of the interventions took place over less than or equal to a 26-week period. Interventions were compared, via network analysis, against usual care (not specifically defined), other interventions, and placebo. The interventions that were found to reduce injurious falls included the following: (1) exercise alone; (2) combined exercise and vision; (3) combined exercise, vision assessment and treatment, and environmental assessment and modification; and (4) combined clinic-level quality improvement strategies (eg, case management, team changes, patient registries, continuous quality improvement, audit and feedback, staff education, and clinician reminders), multifactorial assessment (eg, comprehensive geriatric evaluation) and treatment, calcium supplementation, and vitamin D supplementation (see **TABLE**).

A 2018 systematic review and meta-analysis investigated whether certain interventions alone or in combination reduced injurious falls in adults age 65 years old and older judged to be at average or increased risk of falling and included 62 RCTs (N=35,058).[2] A majority of trials were conducted in Europe with a preponderance of female participants. This review only included community-dwelling older adults and excluded trials solely recruiting participants with specific medical diagnoses (eg, stroke, dementia, Parkinson disease, vitamin D deficiency) and trials of interventions not feasible in (or easily referred from) primary care. Exercise interventions most commonly consisted of three sessions per week that had components of gait, balance, and functional training and lasted on average 12 months. Multifactorial interventions consisted of a comprehensive geriatric or falls risk factor assessment, with treatment interventions and referrals tailored to the patient and managed by the research team. The interventions varied substantially between studies and included components of exercise, nutrition, medication review, and specialty referral. Control groups for most interventions were usual care or usual care plus a minor intervention (eg, social visits or educational material). Meta-analysis of low heterogeneity trials showed that exercise alone reduced the rate of injurious falls (see **TABLE**). For multifactorial interventions, however, pooled data showed no reduction in injurious falls (see **TABLE**). One trial of vitamin D supplementation of 500,000 IU annually showed an increase in injurious falls at 36 months (N=2,258; incidence rate ratio [IRR], 1.2 [95% CI, 1.0–1.3]), whereas another trial of 800 IU daily showed no difference at 24 months (N=204; IRR, 0.84 [95% CI, 0.45–1.6]). When compared with the

TABLE. Interventions to prevent injurious falls in adults 65 years old and older, compared with usual care

Patient setting	Interventions	No. of trials	No. of patients	Outcome measures[a]	Result (95% CI)
Multiple (eg, home, community, clinic, hospital, retirement home)[1]	Exercise alone	54	41,596	OR	**0.51 (0.33–0.79)**
	Exercise and vision assessment	54	41,596	OR	**0.17 (0.07–0.38)**
	Exercise, vision, environmental assessment	54	41,596	OR	**0.30 (0.13–0.70)**
	Clinic-level quality improvement,[b] multifactorial assessment,[c] calcium and vitamin D supplementation	54	41,596	OR	**0.12 (0.03–0.55)**
Community dwelling[2]	Exercise alone	10	4,622	IRR	**0.81 (0.73–0.90)**
	Multifactorial interventions[c]	16	9,445	RR	0.94 (0.85–1.03)

Data from systematic reviews of randomized controlled trials (statistically significant outcomes in bold font).[1,2] [a] Outcome measures <1 favor the intervention. [b] Clinic quality improvement interventions included case management, team changes, electronic patient registries, facilitated relay of information to clinicians, continuous quality improvement, audit and feedback, staff education, and clinician reminders. [c] Multifactorial assessment and interventions consisted of a comprehensive geriatric or falls risk factor assessment, with treatment interventions and referrals tailored to the patient and managed by the research team. IRR=incidence risk ratio; OR=odds ratio; RR=risk ratio.

previously mentioned systematic review,[1] 44 studies were included in both, 22 of which were used in the various meta-analyses (see **TABLE**).

In 2018, the U.S. Preventive Services Task Force (USPSTF) recommended exercise interventions for community-dwelling adults who are 65 years old or older and at increased risk for falls (USPSTF grade B, clinicians should offer or provide this service, based on a high certainty that the net benefit is moderate).[3] The USPSTF recommended that clinicians selectively offer multifactorial interventions for these adults (USPSTF grade C, clinicians should offer or provide this service depending on individual patient circumstances, based on professional judgment and patient preferences, because of the presence of at least moderate certainty that the net benefit is small). The USPSTF recommended against vitamin D supplementation to prevent falls (USPSTF grade D, clinicians should not recommend this, based on a moderate or high certainty that no net benefit or that the harms outweigh the benefit). The USPSTF used the previously mentioned systematic review to arrive at these evidence-based recommendations.[2] EBP

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Which strategies are effective in promoting adherence to repeat-dosing hormonal contraception methods (such as oral contraceptive pills, patches, intravaginal rings, and injections)?

EVIDENCE-BASED ANSWER

Intensive counseling interventions as well as multiple counseling contacts may improve contraception adherence (SOR: **B**, systematic review of low-quality randomized controlled trials [RCTs]). Phone messaging does not improve contraceptive adherence at 12 months after termination of pregnancy (SOR: **B**, single-blind RCT with high attrition). Immediate as opposed to delayed administration of depot medroxyprogesterone acetate in adolescents and young adult women increases continuation at 3 to 6 months (SOR: **B**, single RCT).

DOI 10.1097/EBP.0000000000001068

A 2019 meta-analysis of 10 randomized controlled trials (RCTs; N=6,242) examined strategies to improve adherence to and continuation of repeatedly dosed hormonal contraception compared with usual family planning care or no reminders.[1] Patients were women of reproductive age seeking oral contraceptives (OCs), depot medroxyprogesterone acetate (DMPA), intravaginal ring, or transdermal patch to avoid pregnancy. Follow-up occurred at three, four, six, nine, and 12 months. Six studies (n=2,624) focused on in-person counseling interventions, while four of these (n=1,790) included multiple counseling components, and four studies sent text reminders of next appointment or doses, with or without educational material (n=1,356). No difference was observed in adherence to OCs or DMPA in women receiving text reminders with or without educational information compared with usual care (see **TABLE**). In a subset of six trials, intensive counseling improved contraceptive continuation compared with usual care at 12 months (6 studies, n=2,624; odds ratio [OR] 1.3; 95% CI, 1.1–1.5). Multicomponent counseling did not improve contraceptive continuation (3 trials, n=834). The highest risks of bias included unclear blinding and loss to follow-up. The certainty of results was deemed low.

A 2015 single-blind Cambodian RCT (N=500) included women who sought abortion services at four clinics and assessed the effect of mobile phone–based interventions compared with usual care on post abortion long- and short-acting contraception use.[2] Contraceptive methods included OC, DMPA, subdermal implants, and intrauterine devices. Patients received six interactive voice messages with counselor support sessions in addition to usual care or usual care alone. This study was not included in the meta-analysis above because of inclusion of long-acting methods. Patients in the intervention group self-reported significantly higher rates of use of any of the contraceptive methods at four months compared with usual care (64% vs 46%; relative risk [RR] 1:4; 95% CI, 1.2–1.7), but no difference was noted at 12 months (50% vs 43%; RR 1:2; 95% CI, 0.9–1.5). Continuation rates were not reported by type of contraceptive. Limitations included inability to blind participants and significant attrition (34% lost to follow-up by 12 months).

A 2016 RCT (N=333) examined the effectiveness of administering DMPA at the initial encounter compared with bridging with 21 days of OC, patch, or ring contraceptive before receiving DMPA in sexually active 14 to 26-year-old women recruited from a Family Planning Clinic.[3] The bridging group returned to clinic after 21 days for repeat pregnancy testing and DMPA injection. Follow-up occurred at three and six months after initial injections. The primary outcome was DMPA continuation at six months. Continuation rates were higher at the third injection for women who received immediate DMPA injection compared with the bridge method (30% vs 21%; adjusted OR 2.2; 95% CI, 1.2–4.2). No harms were noted. Generalizability may be limited because of the specific population and no randomization to a conventional DMPA (ie,

TABLE. Effectiveness of counseling or reminders for adherence to or continuation of contraceptive method[1]

No. of studies	No. of patients	Intervention	Comparison	Outcome	OR	95% CI
6	2,624	Counseling	Usual family planning care	Continuation of OC	**1.28**	**1.07–1.54**
1	350	Counseling	Usual family planning care	Rate of discontinuation because of menstrual disturbances	**0.20**	**0.11–0.37**
1	350	Counseling	Usual family planning care	Rate of discontinuation because of other AE	0.73	0.36–1.47
3	1,985	Counseling	Usual family planning care	Pregnancy	1.24	0.98–1.57
1	683	Reminders with education	Usual family planning care	Continuation of OC	**1.54**	**1.14–2.10**
1	250	Reminders without education	Usual family planning care	Continuation of DMPA	0.90	0.55–1.49
1	73	Reminders (+/– education)	Usual family planning care	Adherence to OC as indicated by missed pills	**0.80**	**1.22–2.82**
2	350	Reminders (+/– education)	Usual family planning care	Adherence to DMPA as indicated by on time injections overall	0.84	0.54–1.29

AE=adverse event; DMPA=depot medroxyprogesterone acetate; OC=oral contraceptive; OR=odds ratio. Statistically significant differences are in bold.

waiting to initiate DMPA until onset of menses) group. EBP

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Does a third MMR vaccine in an outbreak area decrease the incidence of mumps in young adults?

EVIDENCE-BASED ANSWER

A third dose of measles, mumps, and rubella vaccine given during an outbreak lowers the risk of mumps by 78% (SOR: **B**, retrospective cohort study). A third dose increases levels of mumps-specific Immunoglobulin G (IgG) and viral neutralization IgG at four weeks and one year (SOR: **C**, small disease-oriented prospective cohort). The Advisory Committee on Immunization Practices recommends a third dose for individuals at risk in an outbreak setting (SOR: **C**, expert opinion).

DOI 10.1097/EBP.0000000000001069

A 2017 retrospective cohort study (N=20,496) on a university campus examined the effectiveness of

a third measles, mumps, rubella (MMR) vaccine at decreasing attack rates of mumps for students between 18 and 24 years old during a mumps outbreak in August 2015 to May 2016.[1] Before the outbreak, 98% of the students had two doses of MMR. The university held eight free vaccination clinics over 10 days in November 2015, during which 23% of students received a third dose. Throughout the outbreak, 259 positive cases were noted. A third MMR vaccine lowered the risk of contracting mumps by 78% (hazard ratio 0.22; 95% CI, 0.12–0.39). The attack rate in those who received a third dose was 6.7 per 1,000 students, compared with 14.5 per 1,000 students with the baseline of two vaccines ($P<.001$). The study was limited by the inability to control for variables such as increased case identification, public health response, or health-seeking behavior.

A 2020 small prospective cohort study examined the antibody response to a third dose of MMR for individuals 18 to 25 years old who had received two prior MMR doses and had no previous history of mumps (N=150, 46% male and 54% female).[2] Blood samples were collected from individuals before vaccination, and again at four weeks and one year. Levels of mumps virus–specific immunoglobulin G (IgG) were determined with fluorescent bead-based multiplex immunoassay. The viral neutralizing capacity, which is ability of an antibody to bind to a virus in a way that not only triggers the immune response but blocks infection, was determined via the focus-reduction neutralization test (ND_{50} titer). The study estimated immunity cutoffs by analyzing pre-outbreak mumps virus-specific antibody levels from individuals who did not get mumps with those who got mumps during outbreaks from 2009 to 2012. A mumps-specific IgG concentration of >102 RU/mL indicated estimated immunity. Before vaccination, 81% of individuals had levels of IgG above the cutoff. After vaccination, the percentage of individuals above the IgG cutoff increased to 94% at four weeks ($P=.001$) and 91% at one year ($P=.026$). For the neutralization assay, a ND_{50} titer of >34 indicated estimated immunity. The ND_{50} titers showed 78% of individuals above the cutoff at baseline. After vaccination, the percentage of individuals above the cutoff increased to 86% at four weeks ($P<.0001$) and 86% at one year ($P=.001$).

A 2018 Advisory Committee on Immunization Practices bulletin recommended a third dose of a mumps containing vaccine be administered to those identified by public health authorities as at increased risk for acquiring mumps because of an outbreak.[3] EBP

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Is cognitive behavioral therapy effective in the treatment of irritable bowel syndrome?

EVIDENCE-BASED ANSWER

Cognitive behavioral therapy (CBT) is more effective than medical treatment alone for irritable bowel syndrome (IBS), improving symptoms by another 10% (SOR: **B**, single randomized controlled trial [RCT]). Patients who receive home-based CBT show greater improvement in IBS symptoms than patients who receive in-clinic education (SOR: **B**, individual RCT). The Canadian Association of Gastroenterology recommends CBT as part of a multimodal treatment plan for IBS per the Canadian Association of Gastroenterology (SOR: **C**, expert opinion).

DOI 10.1097/EBP.0000000000001060

A 2019 multicenter, prospective, three-arm randomized controlled trial (RCT; n=558) assessed

telephone-delivered cognitive behavioral therapy (CBT) and web-delivered CBT versus treatment as usual (TAU) for irritable bowel syndrome (IBS).[1] Patients were recruited from 74 primary care clinics and three specialty clinics in London and the South of England from May 2014 to March 2016. Adult patients were eligible if they fulfilled ROME III criteria for IBS, reported ongoing significant symptoms defined as greater than or equal to 75 on the IBS Symptom Severity Score (IBS-SSS) (ranges 0–500, with higher scores indicating more severe disease), had been offered first-line therapies, and had IBS symptoms for 12 or more months. Patients with unexplained rectal bleeding or weight loss, diagnoses causing symptoms similar to IBS, or those who had received CBT in the past two years were excluded. Patients had a mean age of 43 years old (75.8% female, 91% white) and were randomized into one of three trial arms. Two interventions were assessed: therapist-delivered telephone CBT (TCBT) and a low-intensity web-based CBT (WCBT). All three groups received TAU, with the control group being TAU alone. Patients randomized to the TCBT arm received a detailed self-help manual including homework tasks and had six one hour telephone sessions with a CBT therapist at predetermined intervals. They also received two one hour booster sessions at four and eight months (a total of 8 hours of therapist support). WCBT participants received online access to an established interactive web-based CBT program. They also received three 30-minute telephone therapy calls at predetermined intervals and two 30-minute booster sessions at four and eight months (2.5 hours of therapist support). TAU consisted of continuation of current medications and usual primary care or specialty follow-up with no psychological therapy. The primary outcomes were measurements on the IBS-SSS and Work and Social Adjustment Scale (WSAS); a validated quality of life questionnaire with scores from 0 to 40 (higher scores meaning worse quality of life). Compared with TAU, TCBT and WCBT both had lower IBS-SSS and WAS scores at 12 months (see **TABLE**). A secondary outcome was the Hospital Anxiety and Depression Scale (HADS; range 0 to 12; higher scores meaning worse mood). No serious adverse reactions to treatment were noted. This RCT was limited by reliance on volunteers to participate in CBT which may limit generalizability, relatively few male patients, lack of ethnic diversity, and less than 80% follow-up.

TABLE. Change beyond "care as usual" in patients' irritable bowel syndrome symptoms with telephone and web-based cognitive behavioral therapy[1]

	TBCT (95% CI)	WCBT (95% CI)
IBS-SSS score		
3 months	–69.2 (0.88.7 to –49.7)	–53.0 (–74.9 to 0.31.1)
6 months	–58.3 (–80.3 to –36.3)	–35.7 (–58.5 to –12.9)
12 months	–61.6 (–89.5 to –33.8)	–35.2 (–57.8 to –12.6)
WSAS score		
3 months	–3.4 (–4.8 to –2.0)	–3.0 (–4.4 to –1.5)
6 months	–2.7 (–4.2 to –1.2)	–2.5 (–4.0 to –1.0)
12 months	–3.5 (–5.1 to –1.9)	–3.0 (–4.6 to –1.3)
HADS score		
3 months	–2.1 (–3.2 to –0.9)	–2.5 (–3.7 to –1.3)
6 months	–2.2 (–3.5 to –0.8)	–2.9 (–4.2 to –1.6)
12 months	–2.8 (–4.1 to –1.5)	–2.3 (–3.7 to –1.0)

HADS=Hospital Anxiety and Depression Scale (range 0–21); IBS=irritable bowel syndrome; IBS-SSS=IBS Symptom Severity Score (range 0–500); TCBT=telephone-delivered CBT; WCBT=web-based CBT; WSAS=Work and Social Adjustment Scale (range 0–40).

A 2019 prospective RCT (n=436) assessed improvement in gastrointestinal symptoms after CBT for refractory IBS.[2] Adults 18 to 70 years old were eligible if they suffered from IBS defined by ROME III criteria and symptoms were at least moderately severe (ie, occurred at least twice weekly and caused life interference). Patients were excluded if they presented evidence of alternative gastrointestinal disease, had been diagnosed with malignancy, were undergoing IBS-targeted psychotherapy, had a major psychiatric disorder, or used certain antibiotics during the 12 weeks before baseline assessment. Patients had a mean age of 41 years old (80% female, 89.4% White). Patients were randomized into one of three trial arms: standard CBT (S-CBT, n=146, included 10 weekly, 60-minute sessions), four sessions of primarily home-based CBT requiring minimal therapist contact (MC-CBT, n=145, in which patients received similar home-study materials as S-CBT), or four sessions of IBS education (EDU, n=145) that provided support and information about IBS. The primary outcome was global improvement of IBS symptoms on the IBS version of the Clinical Global Impressions-Improvement Scale (CGI-I),

collected at two weeks, three months, and six months after treatment completion and measured by both patients and gastroenterologists blinded to treatment group. A higher proportion of patients receiving MC-CBT experienced moderate to substantial improvement in gastrointestinal symptoms two weeks after treatment (61% by patient report and 55.7% by gastroenterologist report) than those in the EDU arm (43.5% by patient report and 40.4% by gastroenterologist report; $P<.05$). Gastrointestinal symptom improvement rated by gastroenterologists six months after treatment completion also differed between the MC-CBT and EDU groups (58.4% vs 44.8%; $P=.05$). One adverse event (suicide attempt) was noted that was thought unrelated to the treatment protocol. Study limitations included relatively few male patients, lack of ethnic diversity, reliance on volunteers, lack of placebo, and subjectivity of clinical endpoints.

In 2019, the Canadian Association of Gastroenterology published an evidence-based recommendation regarding the management of IBS.[3] They recommend CBT as part of a multifaceted and individualized approach to treatment of IBS. Per the guideline, this is a conditional recommendation based on low-quality evidence. EBP

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

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How effective is omalizumab as a second-line treatment for chronic urticaria in patients who do not respond to antihistamines?

EVIDENCE-BASED ANSWER

After failing first-line therapy with a second-generation antihistamine up to four times the normal dose, the use of omalizumab is the most effective second-line treatment and can have a complete response as measured by itch severity scores reported by patients (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). The addition of omalizumab to antihistamine treatment regimens can reduce the symptoms of urticaria and increase the number of patients achieving complete relief (SOR: **B**, single RCT).

DOI 10.1097/EBP.0000000000001078

A 2016 meta-analysis (N=1,230) of seven double-blinded randomized controlled trials sought to determine the efficacy and safety of different omalizumab dosing regimens in patients with chronic spontaneous urticaria.[1] Participants included had previously failed various antihistamine regimens and had continued symptoms. Patients were given either a placebo (n=744) or subcutaneous omalizumab, dosed at 75 mg (n=175), 150 mg (n=177), 300 mg (n=506), or 600 mg (n=27). The doses were given once every four weeks, and the duration of the studies ranged from 4 to 28 weeks. Disease characteristics were journaled by patients and then standardized on one of three outcome measurement tools. These tools included the Weekly Itch Score (WIS), the Weekly Wheal Score (WWS), and the Urticarial Activity Score 7 (UAS7). The WIS and WWS are patient-reported disease activity tools both with scores from 0 (no symptoms) to 21 (maximal symptoms), while the UAS7 is a clinical assessment of disease activity with a score of

zero indicating no symptoms and a maximum summative score of 42. When compared to placebo, patients treated with omalizumab were significantly more likely to have a complete response of no symptoms (7 trials, n=245; risk ratio [RR] 4.5; 95% CI, 3.3–6.2). Dosing at 300 mg showed the greatest percentage of complete responders (36%) when compared to other dosing regimens (RR 6.55; 95% CI, 4.17–10.28). Compared with baseline, treatment also significantly reduced both the WIS (weighted mean difference [WMD] –4.7; 95% CI, –9 to –3) and the WWS (WMD –4.7; 95% CI, –7.7 to –1.8). Side effects were minor, and there was not a significant difference reported between patients taking omalizumab or placebo.

A 2013 randomized controlled double-blind study (N=335) evaluated the safety and efficacy of omalizumab in patients with chronic idiopathic urticaria or chronic spontaneous urticaria that were still symptomatic despite an appropriate multidrug regimen.[2] This study was included in the meta-analysis above but is being presented separately because it studies the effect of adding omalizumab to an appropriate multidrug regimen that included H1-antihistamine plus H2- antihistamine, leukotriene receptor antagonists, or both. Patients were randomized in a 3:1 ratio to either omalizumab 300 mg injection once every four weeks for 24 weeks or a placebo injection with an additional 16 weeks of observation after the last dose. The primary outcome was the safety of omalizumab as assessed by adverse events. Efficacy was a secondary outcome and assessed using the itch severity score (ISS), which evaluates the number of hives, size of largest hive, interference with sleep and daily activity, and generates a score from zero (no symptoms or impact) to a maximum of 21. Patients also completed the Dermatology Life Quality Index (DLQI) questionnaire (0 to 30 range, high scores indicating greater impairment) and the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) that ranged from 0 to 100 with greater scores indicating greater impairment. Patients were evaluated at baseline and at weeks four, 12, 24, and 40. The incidence of adverse events over the 24-week course of treatment was similar in the omalizumab group in comparison with the placebo group (65% vs 64%, no *P*-value provided). The mean improvement in ISS from baseline to 12 weeks was statistically significant for the omalizumab group compared to the placebo group (–8.6 vs –4.0, $P<.001$). A significantly greater proportion of patients in the omalizumab group were completely itch and hive free by 12 weeks compared to the placebo group (34% vs 5%, $P<.001$). At 12 weeks, the omalizumab group had significant improvement in both the DLQI (9.7 vs 5.1, $P<.001$) and the CU-Q2oL (29 vs 16, $P<.001$) compared to the placebo group. Benefits of omalizumab remained significant at 24 weeks, but once discontinued, returned to the level of placebo over 16 weeks of observation. EBP

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The authors declare no conflicts of interest.
The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Navy Medical Department, the Navy at large, or the Department of Defense.

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How long can a peripheral IV line be used safely with vasopressive medications?

EVIDENCE-BASED ANSWER

Short duration and low-dose vasopressor use may be safe for use in peripheral IVs; however, the safe duration, dose of vasopressor medication, and location of peripheral IV is unknown (SOR: **C**, retrospective chart reviews, small observational studies, systematic review of case series, and 1 randomized controlled trial).

DOI 10.1097/EBP.0000000000001030

A systematic review of 85 articles (N=270) that compiled results from 84 case studies and series and one randomized controlled trial evaluated extravasation or local tissue injury from both peripheral and central venous catheter (CVC) administration of vasopressors.[1]

Inclusion criteria were case reports, case series, observational cohorts, and randomized controlled trials with adult patients who received vasopressors as part of their medical care. For those patients who received peripheral administration of vasopressors, male patients comprised 54% with a mean age of 53 years old. The most common reason for presenting for medical care was concern for sepsis (45%); 325 local tissue injury (skin ulcer, blister, skin or tissue necrosis, gangrene, and limb ischemia) or extravasation events were present between peripheral and CVC vasopressor administration, 318 of which occurred with peripheral administration. Norepinephrine use accounted for 80.4% of these events. Other vasopressors used included dopamine, vasopressin, epinephrine, terlipressin, phenylephrine, and ephedrine. For both peripheral and CVC-related adverse events, 102 of the 325 events occurred after 24 or more hours of vasopressor administration. The average time of peripheral vasopressor administration to extravasation was 35.2 hours, with a median time of 22 hours), whereas the average time to local tissue injury was 55.9 hours (median time of 24 hours).

A prospective, observational study at a large tertiary center involving 55 patients with shock (83.6% with septic shock) in an emergency room evaluated complications from peripheral vasopressor infusion.[2] The study enrolled 34 males and 21 females with a mean age of 70 years old, and many of them had comorbid conditions to include hypertension, diabetes, and coronary artery disease. Patients who received vasopressors through a peripheral venous catheter (started in the emergency department) were identified for inclusion in the study. Physicians then evaluated the IV sites twice daily while the vasopressor was infused, then once daily up to 48 hours. Complications were defined as minor (drug extravasation, thrombophlebitis, and localized cellulitis) and major (tissue necrosis and limb ischemia). The most common vasopressor used was norepinephrine (90.9% of patients). Dopamine was used in the other 9.1% of patients. Of all the patients included in the study, three (5.5%) had complications, all of which were minor (either local thrombophlebitis or local erythema managed conservatively). The time at which these events occurred ranged from 11 to 40 hours. All occurred in patients receiving norepinephrine (doses ranged from 7 to 19 μg/min) and with 20-gauge catheters. Three patients received two vasopressive agents, of which none had complications.

A single-center, retrospective chart review was performed at a large tertiary center to evaluate the incidence of extravasation events associated with peripheral IV administration of vasopressors and develop a protocol for peripheral vasopressor use.[3] Electronic charts of adult patients admitted to the intensive care unit (ICU) or a stepdown unit during a 16-month period who received a vasopressor agent via a peripheral venous line were reviewed. A formula was used to calculate, in norepinephrine equivalents, the dose of vasopressor at the time of extravasation. On chart review, 202 patients were given peripheral vasopressors in the stepdown and ICU settings, with 340 peripheral IV catheter sites (forearm, antecubital fossa, hand, other) used for vasopressor infusion. Of these patients, eight (4%) had extravasation events, defined as "the extravenous administration of a medication or solution that has the potential for severe tissue or cellular damage into the surrounding tissue," occurring over a median time of 21 hours (with a range of 12–30 hours) and with a median dose of 0.11 μg/kg/min norepinephrine equivalents (no range for extravasation dose provided). Notably, none of these events resulted in significant injury and all were able to be managed conservatively. In seven of the eight patients, peripheral vasopressors were able to be restarted. The study provided limited details for each extravasation event, and the majority of patients were elderly with multiple comorbidities. EBP

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Is intermittent fasting more effective than daily calorie restriction for weight loss in otherwise healthy overweight adults?

EVIDENCE-BASED ANSWER

No, but it seems to be another effective option for weight loss. Diets using intermittent eating schedules in obese or overweight adults are as effective but not more effective for losing weight or maintaining weight loss when compared with continuous daily calorie restriction (SOR: **A**, systematic review of randomized controlled trials [RCTs] and 2 RCTs). Intermittent dieting may be associated with greater muscle loss compared with continuous dieting (SOR: **B**, systematic review of RCTs).

DOI 10.1097/EBP.0000000000001108

A 2018 systematic review and meta-analysis of nine randomized controlled trials (RCTs; n=782) compared the effectiveness of intermittent versus continuous dieting on weight loss and body composition.[1] Patients ranged from a mean age of 40 to 62 years old, were primarily healthy obese (body mass index [BMI] >30 kg/m^2) females but some trials also included overweight (BMI 25–29.9 kg/m^2) patients and those with diabetes. Follow-up ranged from 12 to 52 weeks with a large attrition rate (15–52%). Regular intermittent dieting was defined as 2 to 14 days of caloric restriction (400–1,300 kcal/d) interspersed with periods of weight maintenance or ad libitum eating. Intensified intermittent dieting was defined as periods of caloric restriction (1,000–1,700 kcal/d) interspersed with days of even lower caloric restriction (400–1,000 kcal/d). Continuous dieting was fixed at between 1,000 and 1,650 kcal/d or as a percentage reduction from baseline energy requirement. When compared with continuous dieting, there was no significant difference in weight loss for regular intermittent dieting (6 trials, n=533; mean difference [MD] 0.28 kg; 95% CI, –1.3 to 1.7 kg) and intensified intermittent dieting (3 trials, n=322; MD –1.8 kg; 95% CI, –4.1 to 0.5 kg). There was significantly more loss of lean mass in patients randomized to regular intermittent versus continuous dieting (4 trials, n=322; MD –0.86 kg; 95% CI, –1.6 to –0.10 kg), which may signal loss of muscle mass.

A 2018 RCT (n=322) compared the impact of intermittent energy restriction versus continuous energy restriction on weight loss.[2] Patients were middle aged adults, obese (mean BMI 34 kg/m^2), and majority women (83%). Patients were randomized into three groups: continuous energy restriction (1,004 kcal/d for women and 1,205 kcal/d for men), "week-on-week-off" energy restriction (1 week as continuous energy restriction and one week of regular diet), or "5:2" (502 kcal/d for women and 602 kcal/d for men, for 2 days per week, consecutive or nonconsecutive). After significant attrition of 44% of the initially enrolled patients, there remained 53 participants in the continuous energy group, 44 participants in the week-on-week-off group, and 49 participants in the 5:2 group. For the 146 participants who completed the trial, mean weight loss at 12 months was similar between the continuous, intermittent, and the 5:2 groups (–6.6 kg vs –5.1 kg vs –5.0 kg, P=.2).

A 2017 single-center, three-phase RCT (n=100) compared the effects of alternate-day fasting and daily calorie restriction on weight loss, weight maintenance, and cardioprotection in metabolically healthy adults.[3] Patients had a mean age of 44 years old (86% female and 63% Black) and had average BMI of 34 kg/m^2. Participants were randomized to one of three groups: alternate-day fasting (n=34), daily calorie restriction (n=35), or no-intervention control (n=31). The trial had three consecutive phases: an initial four-week run-in phase, a 24-week weight loss phase, and a 24-week weight maintenance phase. During the initial phase, baseline data were collected, and a weight-maintenance energy requirement was calculated using total energy expenditure (TEE). During the weight loss

phase, the daily calorie restriction group consumed 75% of their TEE between three meals daily, whereas the alternate-day fasting group consumed 25% of their TEE at lunch on "fast days" and 125% of their TEE between three meals on "feed days." During the weight maintenance phase, the daily calorie restriction group consumed 100% of their TEE between three meals daily, whereas the alternate-day fasting group consumed 50% of their TEE at lunch on "fast days" and 150% of their TEE between three meals on "feed days." Although both groups experienced weight loss relative to control, there was no difference between alternate-day fasting and daily calorie restriction (–6% vs –5.3%, $P>.05$). Because of the dropout rate (38% in alternate-day fasting group, 29% in daily calorie restriction group, 26% in control group), the study was underpowered to detect differences at six months. EBP

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In cocaine-dependent adults, is dexamphetamine effective for achieving cocaine cessation?

EVIDENCE-BASED ANSWER

Yes. In adult patients with cocaine use disorder, dexamphetamine therapy reduces cocaine use and increases abstinence rates compared to placebo (SOR: **A**, systematic review of randomized controlled trials [RCTs] and single RCT).

DOI 10.1097/EBP.0000000000001091

A 2016 systematic review of 26 randomized parallel group-controlled trials (n=2,366) assessed the efficacy of several psychostimulant drugs, including dexamphetamine, in cocaine-dependent patients in achieving cocaine abstinence[1]. Abstinence was determined by negative urinalysis in majority of trials included. The mean age of participants was 40 years old, with 75% of participants being men. A subanalysis of four trials specifically examining dexamphetamine (n=282) was identified. Dexamphetamine was dosed variously in these trails: 20 mg sustained release (SR) three times daily; nine days 20 mg immediate release (IR) daily, followed by 60 mg IR daily; four weeks of 15 mg SR daily, followed by 30 mg SR daily; or four weeks of 30 mg SR daily, followed by 60 mg SR daily. Outcomes measured were sustained cocaine abstinence (3 weeks or greater) and total cocaine use reduction. Patients treated with dexamphetamine were significantly more likely to achieve cocaine abstinence compared to placebo (3 trials, n=154; risk ratio 2.0; 95% CI, 1.1–3.5). There was no significant difference in overall cocaine reduction between groups.

A 2016 randomized, double-blind, placebo-controlled trial (n=73) evaluated the effectiveness of dexamphetamine in cocaine use disorder for cocaine cessation[2]. Patients were selected who were at least 25 years

of age (90% male) with treatment-refractory cocaine use, regularly (at least 8 days per month) used crack cocaine via free-basing and were already enrolled in an opioid-assisted treatment center. Patients were excluded if they had severe medical or psychiatric problems, pharmacotherapy with a potentially effective drug for cocaine dependence, or current participation in another addiction treatment trial. Participants were randomly assigned to receive either 12 weeks of daily, supervised prescription of 60 mg oral SR dexamphetamine (n=38), or placebo (n=35) in addition to their co-prescribed methadone and diacetylmorphine with follow-up every four weeks for a total of 12 weeks. Outcomes measured were self-reported days of cocaine use and secondary outcomes included self-reported duration of cocaine abstinence, cocaine negative urine samples in final four weeks, average number of days abstinent in the final four weeks of the study, cocaine cravings, self-reported use of other substances, and medication adherence. There were significantly fewer days of reported cocaine use with the dexamphetamine group compared to placebo (45 days vs 61 days, $P=.03$). Additionally, dexamphetamine use was consistent with longer periods of self-reported cocaine abstinence (18 days vs 6.7 days, $P<.001$), more cocaine negative urine samples within the final four weeks (11 vs 3.9, $P<.001$), and significantly more mean days of abstinence within the final 4 weeks (15 days vs 7.5 days, $P=.03$) compared to placebo. Nonsignificant secondary results included changes in cocaine cravings, self-reported use of other substances, and medication adherence. EBP

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Is turmeric efficacious in treating osteoarthritic knee joint pain in adult patients?

EVIDENCE-BASED ANSWER

When compared against placebo, turmeric may have a moderate to large effect on reducing pain and disability, and may also modestly improve quality of life, in patients with knee osteoarthritis (SOR: **B**, meta-analyses of low-quality and heterogeneous randomized controlled trials [RCTs]). Tumeric does not seem to be more effective than ibuprofen for relieving pain or dysfunction due to knee osteoarthritis (SOR: **B**, meta-analysis of low-quality and heterogeneous RCTs).

DOI 10.1097/EBP.0000000000001088

A 2018 systematic review and meta-analysis of eight randomized controlled trials (RCTs) assessed the efficacy of curcumin (turmeric) in 821 patients with knee osteoarthritis.[1] The patients had an average age of 59.1 years old (mean range 48.5–68.6 years) and were predominantly female (83.6%). Studies ranged in size from 28 to 331 patients, and were conducted in Armenia, India, Iran, Japan, and Thailand. Curcumin dose ranged from 180 mg to 2 g per day; five studies (N=355) used placebo as a comparator and three studies (N=466) used either ibuprofen (800 mg–1,200 mg/d) or celecoxib (200 mg/d). The studies ranged in duration from 4 to 12 weeks. Primary outcomes included pain and function, measured using either a 10-point visual analog scale (VAS) or the Western Ontario and McMaster Universities Osteoarthritis index. Outcomes on these scales were converted to standardized mean differences (SMDs). When compared with placebo, curcumin improved both pain (5 trials, N=331; SMD –0.8; 95% CI, –1.2 to –0.4) and function (3 trials, N=232; SMD –0.5; 95% CI, –0.7 to –0.2). There was no difference between curcumin and ibuprofen for treating pain (2 trials, N=422; SMD –0.05; 95% CI, –0.4 to 0.3)

or function (1 trial, N=331; SMD –0.02; 95% CI, –0.2 to 0.2). The overall quality of the studies was deemed to be very low because of high risk of bias and imprecision of the estimate of the effect, as well as moderate heterogeneity in study design.

A similar 2017 systematic review and meta-analysis found seven RCTs (N=797) investigating curcuminoids for knee osteoarthritis.[2] The patients had an average age range of 50.3 to 68.7 years old. Six of the studies were also included in the previously mentioned systematic review,[1] thus the study locale and curcumin dose range was the same as noted above, with five trials using placebo and two using ibuprofen as comparators. The study durations were from 4 to 16 weeks. In addition to giving pooled SMD results for VAS and Western Ontario and McMaster University Arthritis index criteria (WOMAC) scores for pain and function, the reviewers included the mean difference (MD) in quality of life data, as measured by the Lequesne pain–function index (score range 0–24, with higher scores indicating greater pain and disability). Similar to the previously mentioned meta-analyses, curcumin improved both pain (5 trials, N=366; SMD –3.5; 95% CI, –5 to –2) and function (4 trials, N=498; SMD –3.3; 95% CI, –6.2 to –0.3) when compared with placebo. Curcumin also improved quality of life in placebo controlled RCTs (2 trials, N=107; MD –2.7; 95% CI, –3.5 to –1.9). Of note, heterogeneity was high ($I^2 \geq 95\%$) in meta-analyses for pain and function and was moderate ($I^2 = 50\%$) in the pooled analysis of quality of life. EBP

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Which diet is the most effective for weight loss in patients with the metabolic syndrome?

EVIDENCE-BASED ANSWER

A high-protein low-calorie diet is more effective for weight loss in patients with metabolic syndrome than a standard low-calorie diet (SOR: **B**, single, randomized controlled trial [RCT]). The dietary approaches to stop hypertension diet is just as effective as a low-calorie diet for weight loss but is more effective in treating symptoms of metabolic syndrome (SOR: **B**, single RCT).

DOI 10.1097/EBP.0000000000001104

A 2017 randomized controlled trial (RCT; N=118) assessed the effectiveness of a high-protein diet compared with a standard-protein diet for weight loss in six months of treatment in adults from Mexico with metabolic syndrome.[1] Patients were nonpregnant adults (mean age, 47 years) diagnosed with metabolic syndrome who had a body mass index between 25 and 45 kg/m^2 and no history of psychiatric disorder or bariatric surgery. Metabolic syndrome was defined as central adiposity and possessing any two of the following criteria: reduced HDL, increased triglycerides, high blood pressure, or hyperglycemia. Adults with previous use of weight loss medications, tobacco, alcohol- or drug-dependence treatment, or any change in weight more than 2% within three months before the trial were excluded. Patients were randomized to standard-protein diet (n=59) or a high-protein diet (n=59), which consisted of 0.8 or 1.34 g/kg of protein per day, respectively. Both groups had a 500-calorie restriction per day, were advised to get 150 minutes of aerobic activity per week, and given sample menus and information on their respective diets. The high-protein diet group received meal replacement protein shakes and snack protein bars to accurately track daily protein. Change in weight was the primary outcome measure,

which was measured at baseline and monthly during the six months of this trial. Secondary outcomes were change in laboratory parameters defining metabolic syndrome. After six months, there was a significant difference in weight loss in the high-protein group compared with the standard-protein group (7.0 vs 5.1 kg, $P<.01$). However, no statistically significant difference was observed between the two diets for any secondary outcomes. When restricting results to only those with a 75% or greater adherence to the diet, the difference between groups was even more pronounced with the high-protein group losing significantly more weight than the standard-diet group (–9.5% vs –5.8%, $P<.05$).

A 2005 RCT of 116 adults with metabolic syndrome examined the effectiveness of the dietary approaches to stop hypertension (DASH) diet in promoting weight loss and treating metabolic syndrome.[2] Patients from Iran were included if they met criteria for metabolic syndrome per Adult Treatment Panel III, showed no evidence of cardiovascular disease, smoked, and were not supplementing with any vitamins or minerals. Patients were placed in one of three groups: a weight-reducing diet consisting of 500 kcal restriction with three servings of whole grains per day, a DASH diet consisting of 500 kcal restriction with four servings of whole grain per day, or a control group that ate as they usually did without any intervention. The main outcomes were changes in the components of metabolic syndrome between the eating plans, which were measured at baseline, three months and at six months for each diet, and the prevalence of metabolic syndrome. The components of metabolic syndrome measured were weight, wait circumference, blood pressure, HDL, triglycerides, and fasting blood glucose levels. Patients using the DASH diet experienced significant weight loss compared with baseline for both men (mean difference [MD] –16 kg; $P<.001$) and women (MD –13 kg; $P<.001$). The standard weight-reducing diet group also experienced significant weight loss compared with baseline for both men (MD –13 kg; $P<.05$) and women (MD –12 kg; $P<.05$). The DASH diet also showed a statistically significant reduction in all components of metabolic syndrome ($P<.04$) when compared with the weight-reducing diet, which only reduced two components of metabolic syndrome (waist circumference and triglycerides; $P<.04$). The prevalence of metabolic syndrome decreased significantly in the DASH diet group compared with the weight reduction and control diets group after 6 months (65% vs 81% and 100%; $P<.05$). EBP

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Is forced titration of beta-blockers more effective than usual beta-blocker therapy in improving heart failure with reduced ejection fraction outcomes?

EVIDENCE-BASED ANSWER

Maybe. Patients with heart failure with reduced ejection fraction taking high-dose carvedilol have a lower risk of mortality versus placebo compared with those randomized to lower doses of carvedilol (SOR: **B**, single randomized controlled trial [RCT]). Patients taking higher doses have a lower risk of mortality and hospitalizations compared with those taking lower doses (SOR: **C**, secondary analysis of RCT), but those who tolerate 50% to 99% of the target dose have similar outcomes to those who reach the target (SOR: **C**, single cohort).

DOI 10.1097/EBP.0000000000001107

A 1996 multicenter, randomized controlled trial (RCT; N=345) compared the effect of various doses of

carvedilol with placebo in patients with mild-to-moderate, stable heart failure.[1] Participants were mostly Caucasian men with an average age of 60 years, in New York Heart Association (NYHA) class II and class III heart failure with a mean ejection fraction of 23%. After demonstrating tolerability of carvedilol 6.25 mg twice daily (BID), patients were then randomized to one of four treatment groups: 6.25 mg BID (n=83), 12.5 mg BID (n=89), 25 mg BID (n=89), or placebo (n=84), in which they were titrated and maintained to their assigned carvedilol dose or placebo by mouth. Outcomes measured after a mean follow-up of approximately six months included hospitalizations because of heart failure or other cardiovascular causes, all-cause mortality, and number needed to treat (NNT). Compared with placebo, there was a significant reduction in mortality for the low-dose group (relative risk [RR], 0.36; 95% CI, 0.13–0.998, NNT=11) and the high-dose group (RR, 0.07; 95% CI, 0.01–0.51, NNT=7) but not for the medium-dose group. Although the trial was not powered to perform direct comparisons between dose arms, mortality reduction was greatest in the high-dose carvedilol group. Additionally, all three dosing groups significantly decreased hospitalizations rates compared with placebo (11%, 13%, and 11% vs 22%; $P=.03$).

A 2016 post hoc analysis of a 2009 RCT (N=2,331) compared achieved beta-blocker dose and achieved resting heart rate on all-cause mortality and all-cause hospitalization rates in heart failure with reduced ejection fraction patients.[2] Patients included were stable with a left ventricle ejection fraction (LVEF) of less than 35% and a NYHA class of II, III, or IV. Nonambulatory patients were excluded from the trial. Two beta-blocker groups, high dose (carvedilol ≥25 mg daily or equivalent, n=1,655) and low dose (<25 mg daily or equivalent, n=670), were created for data analysis and followed for a median of 2.5 years. Results were adjusted for confounders, including LVEF, sex, exercise duration, and quality of life. High dose of beta-blocker was associated with a significant decrease in all-cause mortality and all-cause hospitalizations regardless of resting heart rate compared with low dose of beta-blocker (hazard ratio [HR], 0.87; 95% CI, 0.77–0.99). It should be noted that sicker patients who are at a higher risk of death or hospitalization may not be able to tolerate a higher dose, potentially confounding the results.

A 2017 observational trial (N=2,100) studied the effect of ACE-inhibitor/angiotensin receptor blocker and beta-blocker dose on mortality and hospitalizations in adult patients with new-onset or worsening heart failure.[3] Patients (mean age, 68 years) had an LVEF of less than 40% or an elevated brain natriuretic peptide or N-terminal pro B-type natriuretic peptide. Target dosing for patients was metoprolol continuous release/extended release 200 mg daily, carvedilol 25 to 50 mg BID, or bisoprolol 10 mg daily. Patients were broken up into those who achieved the target dose (n=257), 50% to 99% achievement of target dose (n=581), and those who only achieved 1% to 49% of the target dose (n=1,062). After a median follow-up of 21 months, patients who only achieved 1% to 49% of target dose had nearly double the risk of death compared with those who achieved the target dose (HR, 1.9; 95% CI, 1.7–2.1). However, patients who achieved between 50% and 99% of target doses had no significant difference in risk of death or hospitalization because of heart failure as those who reached the target dose (HR, 1.04; 95% CI, 0.89–1.20). EBP

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Does ambulation during first stage of labor reduce the duration of labor and rate of cesarean delivery?

EVIDENCE-BASED ANSWER

Upright positioning (including walking) reduces the duration of the first stage of labor by one hour and 22 minutes and the rate of cesarean delivery by 29% when compared with recumbent positions in women without epidurals (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Walking compared with recumbent positions in women without epidurals reduces labor time by almost four hours (SOR **A**, meta-analysis of RCTs). In primigravid patients, ambulation during the first stage of labor reduces labor time by 42 minutes (SOR: **B,** single RCT). Frequent maternal position changes should be encouraged during labor as long as maternal-fetal monitoring and treatments are not hindered (SOR: **C,** expert opinion).

DOI 10.1097/EBP.0000000000001112

A 2013 meta-analysis of 25 randomized controlled trials (RCTs) from 13 countries, including 5,218 women, studied the outcome of labor in upright and ambulant positions versus recumbent positions during the first stage of labor.[1] The trials included nulliparous, singleton, term pregnancies with either spontaneous or induced labor. Walking, sitting, standing, and kneeling categorized the upright positions, whereas recumbent positions included supine, semirecumbent, and lateral. Patients with and without epidurals were included. In women without an epidural, the overall first stage of labor was shortened by almost one hour and 22 minutes among women in upright positions versus those in recumbent positions (15 trials, N=2,503; average mean difference [MD] –1.4 hours; 95% CI, –2.2 to –0.51 hours, I^2=93%). In comparing walking specifically to various recumbent positions among women without epidural, the first stage of labor was found to be shortened by approximately three hours and 57 minutes in women who walked (3 trials, N=302; [MD]—4 hours; 95% CI, –5.4 to –2.6 hours, I^2=70%). The overall rate of caesarean delivery in women without epidural was lower among women in upright positions than women in recumbent positions (14 trials, N=2,682; relative risk [RR] 0.71; 95% CI, 0.54–0.94; I^2=0%) and also for those who specifically walked versus being in recumbent positions (3 trials, N=306; RR 0.31; 95% CI, 0.12–0.79; I^2=0%). In women with epidurals, the duration of the first stage of labor was not assessed because of variable data for times of events during labor. A subgroup analysis of this group showed no differences in modes of deliveries between women who were upright and ambulant versus those who were recumbent. Note that neither the patients nor the caregivers could be blinded, and the time ambulated varied in each study. In addition, some of the outcomes had significant heterogeneity because of variations in parity, position types, and duration of interventions.

A 2015 RCT evaluated 60 term primigravida women between 16 and 30 years old to assess the effect of ambulation on the first stage of labor and on the outcome of labor.[2] The women were randomly assigned to the experimental (ambulatory) and control group (nonambulatory) with 30 women in each group. Most (93%) of the control group and 83% of the experimental group were between 16 and 25 years old, and 96% of both groups were older than 38 weeks gestation. The study did not mention the use of epidural. Ambulation during the first stage of labor reduced the duration of labor in primigravida women (575 vs 617 minutes, MD 42 minutes; $P<.027$).

In 2017, the American College of Obstetricians and Gynecologists (ACOG) published a committee opinion regarding limiting interventions during labor and delivery.[3] The committee's recommendation concerning maternal positions during labor was based on the above meta-analysis. The ACOG recommended that women need not be restricted to or prescribed one position during labor. Frequent position changes, including ambulation, that help with maternal comfort and fetal positioning was encouraged during labor if adequate monitoring can be performed (no strength of recommendation provided). EBP

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Does having a birth plan influence Cesarean section rates?

EVIDENCE-BASED ANSWER

It is not clear. Written documentation of preferences for options during labor and delivery may be beneficial in decreasing the rate of Cesarean deliveries as mode of delivery in singleton gestations (SOR: **C**, inconsistent cohort and cross-sectional studies).

DOI 10.1097/EBP.0000000000001100

A 2018 prospective cohort study (N=300) examined if the presence of a birth plan was associated with vaginal versus cesarean delivery, interventions, and patient satisfaction.[1] Women meeting inclusion criteria of >34 weeks gestation, cephalic presentation, and a plan to deliver vaginally were identified upon arrival to labor and delivery at a single institution. Women qualified for the study arm if they had a written birth plan, but no further definition was given. Women without a birth plan were the control. There was no significant difference in cesarean delivery rates for women with birth plans compared to control (21% vs 16%; adjusted odds ratio [OR] 1.11; 95% CI, 0.61–2.04). Postpartum satisfaction surveys completed the day of delivery were phrased with affirmative statements per each measure on a scale of 1 to 5 with one being strongly disagree and five as strongly agree. Women with birth plans had lower ratings in all categories; overall satisfaction (4.3 vs 4.8; $P<.01$), experience met expectations (3.3±1.4 vs 4.8; $P<.01$), and felt in control (3.8 vs 4.5; $P<.01$). This study was limited by its non-randomized design and small sample size.

A 2012 retrospective cohort study (N=616) investigated whether introducing a pre-prepared birth plan was associated with a lower risk of cesarean delivery.[2] This institution had a program available for patients to form a birth plan with the help of a midwife who explained various intrapartum considerations. Each birth plan study group patient was matched with control group patients without a birth plan for maternal age, parity, and gestational week at time of birth in a 1:3 ratio. The primary outcome was mode of delivery. Women with prepared birth plans were less likely to have a cesarean delivery (12% vs 20%, $P=.016$). This study was also limited by its non-randomized design and retrospective methodology, raising the risk of confounders.

A 2017 retrospective cross sectional study (N=14,260) assessed if child birth education (CBE) classes, having a birth plan, or both made any difference in the mode of delivery.[3] Women self-reported at the time of admission if they had participated in CBE or prepared a birth plan; neither intervention was further defined within the study. Inclusion criteria were gestation >24 weeks that resulted in a live birth. In the study, 32% of women had attended CBE classes, 12% had birth plans, and 8.8% had both. The control group reported neither. Having a birth plan was associated with a decreased cesarean delivery rate when compared to the control (26% vs 35%, $P<.001$). CBE was also associated with a decrease in cesarean delivery rates (32% vs 35%, $P<.001$). After adjusting for characteristics such as age, parity, gestational age, BMI, and race, a vaginal delivery was more likely for women who participated in CBE classes (OR 1.26; 95% CI, 1.15–1.39), used a birth plan (OR 1.98; 95% CI, 1.56–2.51), or both (OR 1.69; 95% CI, 1.46–1.95). This study was limited by non-randomization, lack of definition for birth plan or CBE, and subjects self-reporting of a birth plan or CBE attendance. EBP

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The authors declare no conflicts of interest.
The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the Air Force at large, or the Department of Defense.

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Does cannabidiol (CBD) oil decrease the frequency and severity of chronic headaches?

EVIDENCE-BASED ANSWER

Although the effect of cannabidiol (CBD) alone is not known, the combination of CBD and tetrahydrocannabinol given daily as prophylaxis may decrease chronic migraine pain by 40% and also have a slight effect on pain and frequency of chronic cluster headaches. (SOR: **C**, single, low-quality randomized controlled trial). However, cannabinoids are not recommended for the treatment of headache (SOR: **C**, expert opinion).

DOI 10.1097/EBP.0000000000001114

A 2017 randomized controlled trial, published only in abstract form, compared cannabidiol (CBD) 9% plus tetrahydrocannabinol (THC) 19% versus amitriptyline for the prevention and treatment of migraine headaches (n=370) and CBD plus THC versus verapamil for the prevention and treatment of chronic cluster headache (n=190).[1] Patients had a normal physical examination and a normal electrocardiogram, but no information was given on demographics, severity of headaches, or duration of headaches. After 10 days of no treatment, those with chronic migraine received prophylactic treatment for three months with either 200 mg/d of CBD/THC in 200 mL 50% fat emulsion or 25 mg/d of amitriptyline. Chronic cluster headache patients received prophylactic treatment with either the same CBD/THC dose or 480 mg/d of verapamil. For acute treatment of headaches, patients could receive an additional 200 mg CBD/THC with 6 mg sumatriptan as a rescue medication. Prophylactic CBD/THC and amitriptyline led to similar decreases in mean pain from migraines on an unknown pain scale (40.4% vs 40.1%; statistical analysis not reported). Change in frequency of migraines was not reported. CBD/THC led to a small decrease in severity and number of cluster headaches but comparison to verapamil and numerical results were not reported. Acute treatment with CBD/THC led to a 43.5% decrease in mean pain at an unknown time point after dosing in a subgroup consisting of patients with migraines and patients with chronic cluster headache and history of childhood migraine (n=not reported). Acute treatment was not effective in decreasing pain in chronic cluster headache patients without a history of childhood migraines.

A 2018 clinical guideline from the Evidence Review Group of the College of Family Physicians of Canada evaluated the use of cannabinoids for pain, nausea/vomiting, spasticity, and adverse events based on a systematic review of the literature.[2] The guideline gave a "strong recommendation" against the use of medical cannabinoids for headache citing lack of evidence and known harm. EBP

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In children with croup, do intramuscular steroids result in faster improvement than oral steroids?

EVIDENCE-BASED ANSWER

No. In children with croup, oral steroids are equally effective as intramuscular dexamethasone in improvement rates, mean time to resolution, emergency department return rates, and need for subsequent treatment (SOR: **A**, consistent results from 3 randomized controlled trials).

DOI 10.1097/EBP.0000000000001106

A 2002 prospective, double-blind, randomized controlled trial (RCT; N=96) evaluated the effect of intramuscular (IM) versus oral dexamethasone for the treatment of moderate-to-severe croup in children.[1] Children 3 to 84 months old with inspiratory stridor or a barky cough and a croup score of two or greater on the Modified Westley Croup scale were randomized to receive a dose of 0.6 mg/kg intramuscular dexamethasone or 0.6 mg/kg oral dexamethasone. Mild croup is a score of 0 to 2, moderate a score of 3 to 5, severe a score of 6 to 11, and impending respiratory failure with a score of 12 to 17 on the Westley Croup scale. Patients were excluded if presenting with signs suggestive of another cause of stridor (ie, epiglottitis, bacterial tracheitis, foreign body, or chronic lung disease), severe comorbidities, inability of the parents to give informed consent, or glucocorticoid therapy within four weeks of presentation. At 24 hours, no significant differences were observed between the IM group compared with the oral group for the proportion with stridor (mean difference [MD] 0%; 95% CI, –27% to 28%), barky cough (MD, –1%; 95% CI, –32% to 26%), expiratory sounds (MD, –2%; 95% CI, –30% to 26%), and normal sleeping patterns (MD, –6%; 95% CI, –32% to 22%).

A 2007 prospective RCT (N=52) evaluated treatment with oral betamethasone versus IM dexamethasone in children 6 months to 6 years old who presented to a tertiary pediatric emergency department (ED) with mild-to-moderate viral croup.[2] The diagnosis of croup was based on the presence of acute stridor with barking cough for 12 to 72 hours. Mild-to-moderate croup was defined as any patient with a Modified Westley croup score of 1 to 11, with 11 indicating more severe symptoms. Children presenting with spasmodic croup, bacterial tracheitis, or other various lung diseases were excluded. Study participants were assigned to receive either dexamethasone IM 0.6 mg/kg (N=26) or oral betamethasone 0.4 mg/kg (N=26). Mean Modified Westley Croup score at baseline was 3.6 for the IM group and 2.0 for the oral group (P=.03). In spite of the baseline difference, no significant difference was found in croup scores for the IM group compared with the oral group (~0 vs ~0 data from graph; P=.018) at four hours. At seven days, no significant difference was observed between groups in in the rate of reexamination by the primary care physician after discharge (69% vs 73%; P=.76) or number of return ED visits (7% vs 4%; P=.22).

A 2002 single-blind, prospective RCT (N=277) examined the effectiveness of IM versus oral dexamethasone for the treatment of moderate croup in an ambulatory setting.[3] Children aged 3 months to 12 years old (median age 2 years old) presenting with current or recent history (within 48 hours) of a barky cough with accompanying stridor or retractions were randomized to receive a single dose of IM or oral dexamethasone. Both IM and oral dexamethasone were given as a single dose of 0.6 mg/kg (maximum 8 mg). Results were obtained by contacting caregivers by phone 48 to 72 hours after steroid administration to assess resolution or persistence of symptoms. No significant difference was observed in symptom resolution of IM group compared with the oral group (54% vs 48%; P=.31). Both groups had similar rates of unscheduled returns (32% vs 25%; P=.12), need for additional treatments including additional steroids (8% vs 9%; P=.81), racemic epinephrine (1% vs 2%; P=.68), and hospital admissions (1% vs 1%; P=1.0). EBP

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Do antihypertensive agents improve outcomes in patients with congestive heart failure with preserved ejection fraction?

EVIDENCE-BASED ANSWER

Probably not. Antihypertensive agents do not reduce hospitalizations or mortality rates compared with placebo in patients with heart failure with preserved ejection fraction (SOR: **B**, 2 randomized controlled trials [RCTs]). There is also no improvement in overall quality of life or physical aerobic conditioning compared with placebo (SOR: **B**, single RCT).

DOI 10.1097/EBP.0000000000001090

A 2008 randomized controlled trial (RCT; N=150) evaluated the effect of irbesartan or ramipril, plus diuretics on patient and disease-oriented outcomes in patients with heart failure with preserved ejection fraction (HFpEF).[1] Patients were adults (mean age 74 years old), with a history of congestive heart failure (CHF) within two months before the recruitment, a New York Heart Association functional class of II to IV, an ejection fraction >45%, and were treated with diuretics 14 days before recruitment. Participants were randomized to three arms: diuretics alone (N=50) or in combination with irbesartan (N=56) or ramipril (N=45). Furosemide or thiazide diuretics were used, with the dosage dependent on the degree of fluid retention. Irbesartan was started at 19 mg daily, titrated to 75 mg at four and eight weeks. Ramipril was started at 2.5 mg and titrated to 10 mg daily. Quality of life, six-minute walk test, and echocardiography were measured at baseline, and then again at 12, 24, and 52 weeks. Quality of life was assessed using the Minnesota Heart Failure Symptom Questionnaire, which uses 21 questions to evaluate how CHF can affect patients on physical, emotional, and socioeconomic levels. Scores range from 0 to 105, with a low score indicating a better quality of life. The six-minute walk test assessed patient's exercise tolerance, by measuring the distance walked in six minutes. At 52 weeks, quality of life scores improved for all groups but there was no significant difference between the diuretic-only group, the irbesartan+diuretic group, and the ramipril plus diuretic group (46%, 51%, vs 50%, $P>.05$). The six-minute walk test increased marginally (average +3–6%) in all groups but was not significantly different among the three groups, and hospitalization recurrence rates were equal in all groups (10–12% in one year, no *P*-value provided). Limitations include slow recruitment because of exclusion of comorbid patients, and some patients were already taking the medicines studied.

A 2003 RCT (N=3,023) investigated the use of candesartan (n=1,514) versus placebo (n=1,509) on hospital admissions and mortality in adult patients with CHF.[2] Enrolled patients (mean age 67 years old) had a preserved ejection fraction of >40% and a New York Heart Association functional class ranging from II to IV for at least four weeks. Patients were excluded if they were not previously admitted for a cardiac cause. The candesartan group was started on either four or eight mg once daily, with the dosage doubling every two weeks. Target dose was 32 mg. Median study duration was 37 months, and three patients in total were lost to follow-up. Primary outcomes measured included death by cardiac arrest and admission to the hospital for CHF exacerbation. Compared with the placebo group, the candesartan treatment group showed no difference in mortality rate because of cardiac arrest (11% vs 11%, $P=.92$). Additionally, there was no significant difference in hospital admission rates because of a CHF exacerbation or death by cardiac arrest for the treatment group versus placebo group (hazard ratio 0.89; 95% CI, 0.77–1.03). Within this subgroup, fewer patients in the candesartan arm had hospital admissions for CHF compared with placebo (15% vs 18%, $P=.047$); however, this difference is very small and considered clinically irrelevant.

Limitations included a shorter treatment period for the study and more follow-up could have been included. EBP

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Does hydrocortisone reduce mortality in mechanically ventilated patients with septic shock?

EVIDENCE-BASED ANSWER

Hydrocortisone does not reduce mortality in mechanically ventilated patients with septic shock but could provide a small reduction in 28-day all-cause mortality to a broader population of patients with septic shock (SOR: **B**, meta-analysis of randomized control trials and single randomized controlled trial). Patients with septic shock should not be treated with hydrocortisone unless hemodynamic stability cannot be achieved with vasopressors and fluid resuscitation (SOR: **C**, based on consensus guideline with low level of evidence).

DOI 10.1097/EBP.0000000000001040

A 2019 systemic review and meta-analysis included five randomized controlled trials (RCTs) comparing the effects of treatment with hydrocortisone to placebo on 28-day all-cause mortality in adult intensive care unit (ICU) patients (N=5,838).[1] Patients were approximately 64 years old and 64% male. The active treatment protocol varied in the studies with two trials using hydrocortisone 50 mg IV every six hours plus fludrocortisone 50 μg via nasogastric (NG) tube for seven days (n=1,570), two trials using hydrocortisone 200 mg daily continuous IV (1 trial for 7 days, and 1 for 6 days with additional 6 day taper; n=3,801), and one trial using hydrocortisone 50 mg IV every six hours for five days followed by a six-day taper (n=499). The percentage of patients on mechanical ventilation ranged from 87.3% to 99.6% in four of the trials and the fifth trial had 54.2% of patients on mechanical ventilation at baseline. Randomization in two of the RCTs (n=419) occurred within eight hours of septic shock diagnosis, and in the other three RCTs, it occurred between 24 and 72 hours. Treatment with hydrocortisone improved 28-day mortality compared with placebo (5 RCTs, N=5,838; 27.1% vs 30.1%; risk ratio=0.92; 95% CI=0.85–0.99). No difference was noted in any secondary outcomes including 90-day and one-year mortality, in-hospital or in-ICU mortality.

A 2018 multicenter, double-blind, RCT included 3,658 adult ICU patients (average age 62 with 61% male) with septic shock requiring vasopressors and mechanical ventilation, examined the effects of a continuous infusion of hydrocortisone 200 mg IV daily compared with placebo for seven days on 90-day mortality.[2] This RCT is the largest study included in the above meta-analysis and is reported separately given that nearly all patients received mechanical ventilation (99.6%). All patients were adults on mechanical ventilation with ≥2 systemic inflammatory response syndrome criteria who had received continuous vasopressors for ≥4 hours before enrollment. No significant difference was observed in 90-day mortality between hydrocortisone and placebo (27.9% vs 28.8%; odds ratio=0.95; 95% CI, 0.82–1.10).

The Surviving Sepsis Campaign released updated International Guidelines for Management of Sepsis and Septic Shock in 2016.[3] Using Grading of Recommendations Assessment, Development, and Evaluation methodology, the evidence-based consensus group recommended against the use of hydrocortisone for septic shock if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability (weak recommendation, conflicting meta-analyses and RCTs). If hemodynamic stability is not achieved, then Surviving Sepsis guidelines recommended

IV hydrocortisone 200 mg daily (weak recommendation, low-quality evidence). The guideline did not differentiate recommendations for patients with or without mechanical ventilation. EBP

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Does azithromycin use increase mortality in adults with underlying cardiovascular disease?

EVIDENCE-BASED ANSWER

No. In patients with underlying cardiovascular disease of many different types, the use of azithromycin in short- or long-term treatment courses does not increase mortality (SOR: **A**, 2 high-quality meta-analyses).

DOI 10.1097/EBP.0000000000001124

A 2018 meta-analysis (N=22,601,032) of 13 randomized controlled trials, 15 cohort studies, and five case-control studies assessed the cardiac safety and efficacy of macrolide antibiotics in patients with a history of cardiovascular disease.[1] Antibiotics were evaluated individually when reviewing occurrences of myocardial infarctions (MIs) and as a class when examining 30-day cardiovascular mortality. Inclusion criteria were broad and included any studies where patients received a macrolide antibiotic for any cause, and a control group was present. Trials were excluded if patients were diagnosed with sepsis or were ever in the intensive care unit (ICU). Treatment duration and follow-up varied greatly with most studies' treatment lasting 14 days to 3 months, and most follow-up being from 90 days to 2 years. Compared with control or placebo, there was no significant increase in likelihood for 30-day mortality for macrolide antibiotics (9 studies, n=18,307,518; odds ratio [OR], 1.2; 95% CI, 0.94–1.6). Azithromycin did not increase the occurrence of MI significantly compared with placebo (21 studies, n=1,681,489; OR, 1.02; 95% CI, 0.87–1.2).

A 2014 meta-analysis (N=15,588) of 12 randomized, double-blinded trials examined cardiovascular events and safety outcomes in adults with chronic heart or lung disease.[2] All patients had taken azithromycin while hospitalized or as an outpatient either for treatment of infection or as secondary prevention of coronary artery disease. The median treatment course was five days (with 2 studies spanning 1 year) with a median dosing of 500 mg daily. All patients were randomized to receive either azithromycin care (with or without standard care) or placebo plus standard care. Outcomes measured included mortality, hospitalization rate, and need for coronary intervention. After pooling nine trials (n=15,492), there was no significant difference in the azithromycin group for risk of mortality (relative risk, 0.88; 95% CI, 0.75–1.02), hospitalizations because of cardiovascular issues (OR 1.0; 95% CI, 0.92–1.1), or need for coronary intervention (OR, 0.99; 95% CI, 0.89–1.1) compared with placebo. One important limitation was the lack of information from some of the trials regarding the cause for rehospitalization when it did occur. EBP

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In adult patients with rotator cuff tears, does surgery, compared with conservative treatments, improve pain and function?

EVIDENCE-BASED ANSWER

Patients with full-thickness rotator cuff tears experience small improvements in pain and function with rotator cuff repair compared with nonoperative treatment (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). In patients with rotator cuff disease without full thickness tears, nonoperative therapies result in less pain at six and 12 months, but there is a small improvement in function in the surgery group at two, five, and 10 years of unclear clinical significance (SOR: **A**, meta-analysis of RCTs).

DOI 10.1097/EBP.0000000000001120

A 2019 meta-analysis of nine randomized controlled trials [RCTs] (N=1,007) assessed rotator cuff repair compared with placebo, no treatment, or any other treatment in adults with full-thickness rotator cuff tears on pain and function.[1] The population was 29% to 56% female and mean ages of 56 to 68 years old. Patients had symptoms for several months or years and were diagnosed with rotator cuff tears based on clinical history, physical examination, and imaging (magnetic resonance imaging, ultrasound, or arthrogram). The surgical group had rotator cuff repair with or without subacromial decompression or debridement. Controls included placebo, no treatment, or nonoperative therapy (exercises with or without glucocorticoid injection). Primary outcomes were pain and function at six months, 12 months, >12 months, and five years. Mean pain (measured from 0 to 10, 0 is best) was slightly improved at six months, 12 months, >12 months, and five years in the surgery versus nonoperative group (2 studies, n=207; mean difference [MD] –1.1; 95% CI; –2 to –0.22; 3 studies, n=258; MD –0.87; 95% CI, –1.3 to –0.43; 2 studies, n=212; MD –0.76; 95% CI, –1.2 to –0.32; and 1 study, n=103; MD –0.87; 95% CI, –1.58 to –0.42). Mean function (measured from 0 to 100, 100 is best) was minimally improved at 12 months in the nonoperative group versus surgery group (3 studies, n=269; MD 6; 95% CI, 2.4–9.5), but there was no difference at six months, >12 months, and five years. No serious adverse events were reported in the trials. Authors concluded that it is uncertain if rotator cuff repair surgery provides clinically meaningful benefits in people with symptomatic rotator cuff tears. A limitation of the study was that there were no subgroups of young athletes that required higher levels of functioning following treatment.

A 2019 meta-analysis of eight RCTs (N=1,062) examined the effects of subacromial decompression surgery with placebo, no treatment, or any other nonsurgical interventions in adults with rotator cuff disease, all with subacromial impingement (excluding full thickness tears).[2] There was no overlap in studies included between this and the previous meta-analysis. Mean ages were 42 to 65 years old, and almost all studies had a small female predominance. Patients had rotator cuff disease manifesting as subacromial impingement, and patients with a calcific tendinopathy and full-thickness rotator cuff tear were excluded. The primary outcomes included improvement in pain and function. Mean pain (measured from 0 to 10, 10 indicating most pain) did not differ between surgery and exercises only at three months, two years, five years, and 10 years. At six months and one year, however, there was a modest improvement in the exercise versus the surgery group (4 studies, n=399; effect size [ES] –0.56; 95% CI; –1.1 to –0.02 and 3 studies, n=316; ES –1.01; 95% CI, –1.6 to –0.42). Compared with no treatment, surgery improved pain at six and 12 months (1 trial, n=177; MD –0.8; 95% CI, –1.6 to –0 and 1 study, n=166; MD –1.2; 95% CI, –2 to –0.36). Mean function (measured from 0 to 100, 100 indicating better function) was no different between surgery and exercise groups at three, six, and 12 months, but function improved in the surgery group over the exercise group at two, five, and 10 years (5 studies, n=467; MD 4.9; 95% CI, 0.77–9.1; 2 studies, n=157; MD 7.6; 95% CI, 0.17–15; and 2 studies, n=156; MD 9.5; 95% CI, 1.9–17). In the RCTs comparing surgical decompression with placebo and no treatment, there were no reports of serious adverse events, but there were increased minor adverse events, including frozen shoulder, brachial swelling from a brachial plexus block, and aggravation of low back pain (2 studies, n=406; relative risk 0.91; 95% CI 0.31–2.65). A limitation of the study was that there were no subgroups studied including elderly and manual workers. EBP

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Is L-theanine effective in decreasing subjective stress levels and improving physiological markers of the stress response?

EVIDENCE-BASED ANSWER

L-Theanine may improve subjective stress and salivary cortisol for short term, but the minimal improvements in subjective and physiologic outcomes are not long lasting and of questionable clinical significance (SOR: **B**, small, randomized controlled trial [RCT]). Acute blood pressure increases in response to mental tasks were attenuated in certain groups with administration of L-theanine without difference in subjective stress (SOR: **C**, disease-oriented outcomes from small RCT).

DOI 10.1097/EBP.0000000000001103

A 2016 crossover, randomized controlled trial (RCT; N=34) examined the effects of L-theanine on serum cortisol levels and subjective stress.[1] Patients were 18 to 40 years old, required to be nonsmokers and free of major illness. Patients were excluded if they presented with any head injury, epilepsy, stroke, or diseases that could affect food metabolism (ie, food allergies, kidney, or liver disease). Stress and fatigue were subjectively measured by a 0 to 100 visual analog scale (VAS, higher scores indicating more stress/fatigue), and mood was measured with the State Trait Anxiety Inventory (STAI-S; 20 item, 1 to –4 Likert scales with total score ranging from 20 to 80, higher score indicating higher current anxiety state). Researchers also measured salivary cortisol levels before and at one and three hours after the completion of a multitasking framework used to induce stress via mathematical processing, memory search, and psychomotor tracking tasks. Participants ingested a nutritional supplement containing 197 mg L-theanine with 1 mg D-theanine (n=17) or placebo containing less than 1 mg of both L- and D-theanine (n=17) at the time of the stress-inducing task. When compared with placebo, participants receiving L-theanine had significantly lower subjective stress levels at one hour post stress-inducing task (mean difference [MD] –3; $P<.01$), but no significant difference at 3 hours (MD –0.3; $P>.05$). The L-theanine group had no significant difference in mood change on STAI-S compared with placebo at one-hour post stress-inducing task (MD –3.3; $P=.20$) or at three hours (MD –1.12; $P=.25$). Salivary cortisol levels were not significantly different among groups post one hour but were significantly lower in the group receiving L-theanine at three hours post task.

A 2012 randomized, crossover, placebo-controlled trial investigated the effects of L-theanine and caffeine on blood pressure under physical and psychological stress.[2] A total of 16 patients (2 subsequently excluded because of absence), eight women and eight men, ages 20 to 24 years, were involved. Patients (n=14) served as their own control and were given either L-theanine (200 mg) + placebo, caffeine (100 mg) + placebo, or placebo only. Patients waited for a seven-day washout, then were reassigned to different group and testing repeated. Psychological stress was induced by oddball target detection tasks and an arithmetic mental task, whereas physical acute stress was induced by cold pressor test (immersion of hand in ice water for 1 minute). Stress was subjectively measured via a VAS (no range reported) and a Profile of Mood States (POMS) examination. The POMS measures different mood behavior responses and ranks scores in tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment (ranges not defined). Researchers also measured arterial blood pressure and skin temperature before, during, and after testing. Stress induction after placebo was noted to increase systolic blood pressure 9 to 34 mmHg within three minutes for a subset of patients termed the high-response group (n=7) whose response to physical stressors was evaluated separately from the low-

response group (n=7). Analysis of variance (ANOVA) revealed significant attenuation in systolic blood pressure increase during tests of psychologic stress in the high-response group after receiving L-theanine in three active testing phases but no significant attenuation with caffeine or placebo. There were no significant effects on blood pressure in the low-response group with L-theanine or caffeine compared to placebo. There were no significant differences in any subjective outcomes measured by either VAS or POMS except a significantly lower score in the L-theanine group versus placebo only in the subscore of tension-anxiety (1.0 vs 6.2; *P*=.004) EBP

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Is exercise an effective treatment for dysmenorrhea?

EVIDENCE-BASED ANSWER

Yes. Participation in exercise such as yoga or aerobics is associated with modest reduction in pain intensity and duration for women with primary dysmenorrhea compared to patients who do not engage in exercise (SOR: **B**, 1 systematic review and 1 meta-analysis of low-quality trials).

DOI 10.1097/EBP.0000000000001138

A 2019 systematic review of 10 low-quality randomized controlled trials (RCTs) assessed the safety and effectiveness of exercise for women 15 to 49 years old with moderate-to-severe primary dysmenorrhea interfering with activities or high baseline scores on a validated pain scale (N=754).[1] Exercise varied widely across studies from low intensity (eg, yoga) to high intensity (eg, aerobics) and for most studies occurred at least three times per week for 10 to 60 minutes each episode. Two RCTs included fewer than three episodes per week (n=135). Study duration ranged from eight weeks to seven months. Women with irregular menstrual cycles, intrauterine devices, mild, infrequent, or secondary dysmenorrhea due to fibroids, endometriosis, or other identifiable causes were excluded. In a subset of nine RCTs (n=632) comparing exercise to no exercise, there was a significant, large pain reduction in the exercise group with a standardized mean difference of –1.9 (95% CI, –2.1 to –1.7), corresponding to 2.5 cm reduction on a 10 cm visual analogue scale (VAS), compared to no exercise. One RCT (n=122) compared exercise to 250 mg of mefemanic acid, given every eight hours from the onset of menstruation until pain relief over two cycles. There was a larger reduction in self-reported pain in the exercise group compared to 250 mg mefenamic acid (mean z-score difference –7.4, 95% CI, –8.4 to –6.4). Limitations included lack of follow-up beyond the end of the intervention, small sample sizes, inconsistent blinding, and inconsistent study protocols.

A 2018 systematic review and meta-analysis of 15 RCTs examined the effectiveness of physical activity for primary dysmenorrhea (N=1,576).[2] Six of the studies (n=637) were also included in the 2019 systematic review. Studies excluded from the review above but included in this systematic review had no active intervention, combination interventions, included women with irregular cycles, or were cluster randomized trials. Patients were nonathlete women 15 to 25 years old with regular menses and not using hormonal contraception. Exercise included aerobic exercise (3 RCTs; n=143), stretching exercises (4 RCTs; n=368), yoga (3 RCTs; n=100), Kegel exercises (3 RTCs; n=46), and mixed interventions (stretching, jogging, relaxation; 1 RCT, n=160). Comparison groups included patients receiving no exercise, acupressure, ibuprofen, hot pack, mefenamic acid, or education. Studies lasted 4 to 12 weeks. Frequency of most exercise interventions was three times per week. Exercise significantly reduced pain intensity compared to controls measured by VAS (0–10 cm) with a pooled effect estimate of –1.9 cm (95% CI, –3.0 to –1.1). According to the authors, greater than 1 cm change on VAS is considered clinically significant. Exercise also reduced pain duration during each menstrual

cycle relative to comparison groups with a pooled estimate of effect of –3.9 hours (95% CI, –4.9 to –3.0). Limitations included heterogeneity of interventions and measurement of pain and inclusion of low-quality studies with high risk of bias. EBP

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What is the optimal pharmacologic VTE prophylaxis in the hospitalized dialysis patient?

EVIDENCE-BASED ANSWER

In critically ill patients with end-stage renal disease, no significant difference was observed in deep venous thrombosis, venous thromboembolism (VTE), and major bleeding between dalteparin and unfractionated heparin (UFH) (SOR: **B**, multicenter blinded randomized controlled trial). Enoxaparin may be as safe and effective as UFH for VTE prophylaxis in medically ill patients on hemodialysis (SOR: **B**, single-center retrospective cohort study).

DOI 10.1097/EBP.0000000000001116

A 2018 multicenter randomized controlled trial in Canada compared the low molecular weight heparin dalteparin 5,000 IU daily with unfractionated heparin (UFH) 5,000 IU twice-daily for the prevention of venous thromboembolism (VTE) in critically ill patients.[1] The primary outcome was major bleeding, pulmonary embolism (PE), and any VTE.[1] The two subgroups of the trial were intensive care unit (ICU) patients already on hemodialysis (HD) before admission (n=118) and severe renal disease on admission to the ICU (the 118 end-stage renal disease (ESRD) patients plus nondialysis dependent with creatinine clearance <30 mL/min, n=590). The inclusion criteria were adults greater than 45 kg and expected ICU stay of greater than 72 hours. In patients with ESRD, no significant difference was seen between the patients who received dalteparin versus UFH in any VTE (10.0% vs 6.4%, *P*=.39) or major bleeding (5.0% vs 8.6%; *P*=.32). When the ESRD cohort data were combined with the severe renal disease patients (n=590), no difference was seen in bleeding events or any VTE; however, there was an increase in proximal deep venous thrombosis (DVT) in the dalteparin group when compared with the UFH group (7.6% vs 3.7%; hazard ratio 0.47, 95% CI, 0.11–2.08, *P*=.04).

A 2017 single-center retrospective cohort study (N=225) evaluated whether bleeding events differed between patients at a community hospital who received HD with at least two consecutive days of concomitant VTE prophylaxis with enoxaparin 30 mg daily or UFH 5,000 units every eight hours.[2] One hundred-fifty patients were evaluated chronologically in the UFH cohort. There were 75 patients in the enoxaparin cohort. Patients on UFH were excluded if they received less than two days of prophylaxis. Also, excluded were patients who were in the ICU, received continuous renal replacement therapy, peritoneal dialysis, or surgery at any point during the hospitalization. The characteristics between the two groups were similar with a mean age of 67, and most were White men. The primary outcome was bleeding events attributed to enoxaparin or UFH during the hospitalization, which were assessed as major, clinically relevant nonmajor, or minor. Major bleeding was defined as fatal bleeding or symptomatic bleeding in a critical area or organ, and clinically relevant nonmajor bleeding was defined as bleeding not meeting the criteria for major bleeding but required intervention. Any bleeds that did not meet requirements for the first two were considered minor bleeds. The secondary outcomes were occurrence of confirmed DVT or PE during admission. At the end of the study, enoxaparin and UFH were equivalent for bleeding risk, and enoxaparin was noninferior in

thrombosis (risk ratio 0.77, 95% CI, 0.49–1.22; $P=.04$ for noninferiority). EBP

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Do any treatments for hyperlipidemia in children improve cardiovascular disease markers or risk factors?

EVIDENCE-BASED ANSWER

In children with familial hypercholesterolemia, statin use is associated with a reduction in carotid intima-media thickness progression (SOR: **C**, randomized controlled trial [RCT] of disease-oriented evidence). Treatment with flaxseeds likely does not reduce total cholesterol levels and potentially elevates HDL and triglycerides (SOR: **C**, RCT of disease-oriented evidence).

DOI 10.1097/EBP.0000000000001029

A 2009 randomized controlled trial (RCT; N=186) evaluated the continuing effects of statin therapy on carotid intima-media thickness.[1] This study was a continuation of a previous two-year study demonstrating significant regression of carotid intima-media thickness using pravastatin 20 to 40 mg for two years. This trial included children (8 to 18 years old) from a single center who had a parent with clinical or molecular diagnosis of familial hyperlipidemia, had been on fat-restricted diet for at least three months, had an LDL-C ≥72 mg/dL, triglyceride levels <72 mg/dL on two occasions, adequate contraceptive use, and was not treated for hypercholesterolemia. The primary outcome was the change in carotid intima-media thickness compared with the age of statin initiation. After completion of the previous trial, all children (in both the previous intervention and the placebo groups) were treated with pravastatin 20 mg if <14 years old or 40 mg if >14 years old. All children were monitored regularly for lipids and safety parameters (once or twice a year). Carotid intima-media thickness (IMT) was measured by ultrasound at initiation of treatment and at least two years after completion of the placebo controlled trial. Multivariate analysis demonstrated that statin therapy was associated with less carotid IMT progression in the setting of initial small combined carotid IMT (regression coefficient [SE] 0.45, $P<.001$), earlier age of statin initiation (SE 0.003, $P=.016$), male sex (SE 0.03, $P<.001$), and longer duration of statin use (SE 0.01, $P<.001$). Statin therapy resulted in no cardiovascular complaints, cardiovascular events, serious laboratory adverse events, or effects on development. Limitations included enrolling only children with familial hyperlipidemia, inability to evaluate cardiovascular outcomes, and lack of a control comparison in the follow-up study.

A 2009 double-blind RCT (N=32) evaluated the efficacy of flaxseeds for the treatment of hyperlipidemia in children.[2] The trial included children (8 to 18 years old) with a baseline LDL between 135 and 193 mg/dL and a positive family history of hypercholesterolemia. Patients with secondary cause of hyperlipidemia, on cholesterol-lowering drugs, or had surgery in the last three months were excluded. Participants were initially evaluated by a dietician via a self-reported food diary and a fasting lipid panel. The intervention group (n=16) received two ground flaxseed muffins and one slice of ground flaxseed bread totaling 30 g of ground flaxseed daily. The control group (n=16) received two whole wheat muffins and one slice of whole wheat bread daily. Participants in both groups were instructed to eat one muffin for breakfast, one muffin as an afternoon snack, and one slice of bread as an evening snack daily for a four-week period in place of cholesterol-lowering pharmacologic agents. Participant compliance to the diet was not statistically different between groups. The primary outcomes of the change in total cholesterol, HDL, triglyceride and LDL levels were measured after four weeks of treatment. A diet including flaxseed did not change total cholesterol (–8.5

mg/dL; 95% CI, –22 to 4.3 mg/dL) or LDL (–7 mg/dL; 95% CI, –17 to 2.7 mg/dL), but decreased HDL (–7.4 mg/dL; 95% CI, –3.1 to –11.6 mg/dL) and increased triglycerides (+29 mg/dL, 95% CI, 4.4 to 53 mg/dL) compared with baseline values. EBP

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Is collaborative decision making and goal setting effective in the treatment of type 2 diabetes mellitus?

EVIDENCE-BASED ANSWER

Shared decision making improves patients' confidence in their own decision-making ability by about 6% (SOR: **A**, meta-analysis) but has not been shown to consistently improve other patient-oriented or disease-oriented outcomes, such as glycemic control, blood pressure, lipid control, patient satisfaction, or medication adherence (SOR: **A**, meta-analysis and randomized controlled trial).

DOI 10.1097/EBP.0000000000001057

A 2017 meta-analysis (N=2,292) evaluated the effects of shared decision making (SDM) and its effects on glycemic control using A1c, quality of life, patient knowledge, decision quality, risk perception, patient satisfaction, trust of physician, and medication adherence in the treatment of patients with type 2 diabetes.[1] This meta-analysis included 13 randomized controlled trials, one quasi-experimental study, and two prospective cohort studies. Experimental studies contributed 1,759 patients, and observational studies contributed 537. Of the above incorporated investigations, the only variable that showed consistent improvement was decision quality as measured by the Decisional Conflict Scale, a validated questionnaire scored from 0 to 100, with lower scores indicating less decisional conflict, that assesses the patients' confidence regarding decision making (mean difference, –5.74; 95% CI, –10.63 to –0.85). While individual studies had various positive outcomes for different interventions, no consistent differences were observed in the pooled analysis for the SDM group compared with the controls. A limitation of the analysis was heterogeneity of SDM interventions that may account for the lack of positive outcomes in the pooled analysis.

A 2017 randomized controlled trial (N=153) evaluated the implementation of SDM on attainment of treatment goals in patients with type 2 diabetes, including A1c, lipids, and blood pressure.[2] This study was a cluster randomized trial with intention-to-treat analysis. Patients were 60 to 80 years old with known type 2 diabetes mellitus for 8 to 12 years recruited from 35 Dutch private practices participating in a prior trial (comparing outcomes in patients assigned to intensive diabetes care vs less intensive national guideline based care). The intervention group was subdivided into self-chosen high-intensity or low-intensity treatment targets through SDM that incorporated cardiovascular event risk as well as glycemic control. Patients in the intervention group also prioritized their treatment goals. Patients in the control group continued to receive usual care with the same high-intensity or low-intensity treatment targets (from the prior trial) but with no formal SDM or verbalized prioritization. Follow-up was scheduled at 24 months for assessment of treatment target attainment. Treatment targets were listed as HbA1c 6.5 or 7.0, blood pressure 120 or 140 mmHg systolic, and total cholesterol 135 or 174 mg/dL. At the conclusion of the study, a nonsignificant increase was noted in the proportion of patients achieving all three treatment targets in the intervention group (31.8%) as compared with (25.3%) in the control group (relative risk 1.26; 95% CI, 0.81–1.95). It was hypothesized that the significance of these findings may have been limited by the high proportion of patients (24%) who had already achieved treatment goals at the outset of

the study and by the already high level of diabetes mellitus care in the healthcare system. EBP

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

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When used as the initial induction agent, does oral misoprostol compared with oxytocin shorten the time to vaginal delivery in rupture of membranes before labor at term?

EVIDENCE-BASED ANSWER

No. In women with rupture of membranes before labor, oral misoprostol is no more effective in achieving delivery in 24 hours (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]) or reducing overall duration (SOR: **B**, single RCT) than oxytocin. No difference is noted in rates of cesarean delivery between misoprostol and oxytocin (SOR: **A**, meta-analysis of RCTs and 1 RCT).

DOI 10.1097/EBP.0000000000001055

A 2014 systematic review and meta-analysis (n=13,793) of 75 randomized controlled trials (RCTs) evaluated the effectiveness of oral misoprostol for induction of labor.[1] A subanalysis of three RCTs (n=265) comparing the rates of vaginal delivery not achieved within 24 hours when either oral misoprostol or oxytocin was used as the initial induction agent in rupture of membranes before labor was identified. Inclusion criteria were all women greater than 37 weeks' gestation with ruptured membranes (spontaneous or artificial). Misoprostol dosing differed between trials with one trial using 100 μg every six hours up two doses, another trial using 75 μg every four hours with no upper limit of doses, and the third trial using a titrated oral solution hourly, starting at 5 μg. The first two trials used the same oxytocin protocol starting at 2 mU/min, increasing every 20 to 30 minutes (3rd trial no protocol information given). No significant difference was noted in the rates of vaginal delivery not achieved in 24 hours with use of oral misoprostol compared with oxytocin (risk ratio [RR] 0.95; 95% CI, 0.56–1.6). A second subanalysis of six studies (n=765) comparing the rates of cesarean delivery and uterine hyperstimulation between oral misoprostol and oxytocin was also performed. Misoprostol dosing ranged between 50 and 100 μg every 4 to 6 hours, but the IV oxytocin protocols were comparable in all studies, starting at 1 to 2 mU/min and increasing every 15 to 30 minutes. No significant difference was found in rates of cesarean delivery (RR 0.92; 95% CI, 0.66–1.3) or uterine hyperstimulation with fetal heart rate changes (RR 1.0; 95% CI, 0.33–3.1) when comparing patients treated with oral misoprostol versus IV oxytocin.

A 2017 two-centered RCT (n=270) compared sublingual misoprostol to oxytocin as the initial induction agent in prelabor rupture of membranes.[2] Patients (mean age 26 years old) with singleton pregnancies between 37 weeks' and 42 weeks' gestation presenting with prelabor rupture of membranes and Bishop scores ≥6 were included. Exclusion criteria included those who were contracting greater than three times in 10 minutes, FHR abnormalities, and potential cephalopelvic disproportion. Women were assigned to receive either sublingual misoprostol 25 μg every four hours or IV oxytocin starting at 2 mU/min and increasing every 20 minutes. Thirty women who required oxytocin infusion after receiving misoprostol were excluded from the analysis, resulting in 120 women in the misoprostol group and 120 women in the oxytocin group. This exclusion differs from the trials in the

first reference, which included studies that used oxytocin after misoprostol administration. The primary outcome measured was the mean duration from start of induction to onset of active labor, defined as regular contractions with cervical dilation greater than 5 cm. Secondary outcomes measured were duration of the active phase, duration of the second stage, and side effects of misoprostol and oxytocin. The original publication appeared to have transposition errors in tables one and two and discrepancies between the tables and text in the results section. However, the outcomes appear accurate. No significant difference was noted between the mean time from start of labor induction to the start of active labor when either misoprostol or oxytocin (249 vs 230 minutes, $P=.44$) was used. When comparing the mean duration of labor stages, the misoprostol group had significantly shorter times in active labor (480 vs 600 minutes, $P=.04$) and in second stage (48 vs 57 minutes, $P=.03$) compared with the oxytocin group. No difference was noted in the occurrence of cesarean deliveries between the two groups (24 vs 24 cases, $P>.05$). However, side effects of tachysystole (14% vs 5.8%, $P=.02$) and nausea or vomiting (23% vs 0.8%, $P<.01$) did occur more significantly in the misoprostol group compared with the oxytocin group. Study limitations included lack of blinding, failing to use intention-to-treat analysis, and the reporting errors found in the text and tables. EBP

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What is the most effective tapering method for weaning chronic opioid therapy in noncancer pain patients?

EVIDENCE-BASED ANSWER

It is not clear. Sequential opioid tapering may not be effective at successfully weaning off opioid use given a very low success rate of 7% (SOR: **C**, secondary outcomes from small randomized controlled trial). Tapering methods should be individualized based on length of opioid usage, dose, opioid use disorder, and comorbid mental health conditions (SOR: **C**, 2 evidence-based guidelines).

DOI 10.1097/EBP.0000000000001064

A 2018 prospective, Danish single-center, open-label, parallel-group two-phase randomized controlled trial (RCT; N=75) evaluated the efficacy of stabilizing opioid therapy followed by a tapering program in chronic noncancer pain patients[1]. Patients were recruited from a waiting list for a Danish pain center that had a mean age of 51 years old. Participants had pain for six months or longer and were on oral opioids for three months or longer (greater than or equal to 60 mg morphine equivalent/d). Patients who were pregnant, encephalopathic, with hepatic and or renal failure, or had cancer were excluded. Phase one for all patients included stabilization of opioid usage to regular and clockwise sustained release opioids for optimal pain relief. In phase two, patients were randomized to a control group of no changes to current medical treatment (N=20) or a taper off group (N=15) reducing opioid dose by 10% until discontinuation. Patients with difficulties with weekly dose reductions were switched to biweekly. Primary outcomes measured were cognitive function including Continuous Reaction Time, Finger Tapping Test, Digit Span Test, Trail Making Test B, and Mini-mental State Examination. Secondary outcomes included pain

intensities, rest sensation (assessed by patients answering as feeling rested or not), depression, anxiety, opioid misuse, and opioid withdrawal symptoms. During phase one, assessments were completed at baseline and after stabilization (first and second assessments). In phase two, patients were assessed in intervals of 2 to 3 weeks for the third and four assessments, then monthly for the fifth through ninth assessments. Because of a significant dropout rate, only the first four assessments were used in the statistical analysis. Phase two primary outcomes showed no significant differences on the multiple measures of cognitive function and secondary outcomes showed intervention group patients felt significantly more rested, reported as a subjective measurement, at the third assessment (35% control vs 80% intervention, $P=.0082$). Only one patient was able to be weaned off all opioids successfully. The study suffered from over half of the participants dropping out.

The 2017 Clinical Practice Guidelines for opioid therapy from the Veterans Administration and Department of Defense recommended tapering dosages instead of abrupt discontinuation in patients in long-term opioid therapy (strong recommendation, based on RCT and cohort studies).[2] A gradual taper dose reduction of 5% to 20% every four weeks for patients who have been on very high opioid doses was recommended although physicians were advised to consider a more rapid taper with dose reductions weekly in higher risk populations. Per the guidelines, insufficient evidence exists to recommend for or against specific tapering strategies and schedules.

A 2015 evidence-based position paper from the Mayo College of Medicine recommended that rapid tapering should be reserved for only those in inpatient hospital settings with significant coexisting psychiatric or medical illnesses (based on "limited evidence").[3] It further recommended that patients on high-dose opioid therapy for greater than two years should be tapered at monthly intervals (no grade). EBP

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Is methotrexate an effective treatment for patients with fibromyalgia?

EVIDENCE-BASED ANSWER

Methotrexate might be of benefit in patients with refractory fibromyalgia, although with the risk of toxic side effects (SOR: **C**, small case series). International fibromyalgia societies, however, do not mention this medication in their guidelines.

DOI 10.1097/EBP.0000000000001086

A 2014 case series examined the effectiveness of low-dose methotrexate for the treatment of severe refractory fibromyalgia.[1] Two women (47 and 50 years old) with several years of multiple chronic pain sites without laboratory evidence of rheumatologic disease were diagnosed with severe fibromyalgia that did not respond to treatment with NSAIDs, antiseizure medications, antidepressants, and opioids. After failing other medication classes, both patients were started on low-dose methotrexate. Patient A received methotrexate 2.5 mg three times weekly, and patient B received methotrexate 2.5 mg twice weekly. They both increased to 2.5 mg four times weekly with daily folic acid supplementation. Outcomes were measured by the Stanford Health Assessment Questionnaire Disability Index, which ranges from 0 (no incapacity) to 3 (full incapacity) with score above 1.5 indicates severe

TABLE The results of questionnaire scores for each patient with fibromyalgia after treatment with methotrexate[1]

Patient	HAQ-DI	Pain score	Fatigue index	Well-being score	CRP level (normal <10 mg/L)
Pt A	1.8>1.0 (Δ44%)	10>4 (Δ60%)	10>2 (Δ80%)	0>5	23.6>1.9 (Δ92%)
Pt B	1.6>0.5 (Δ68.6%)	10>2 (Δ80%)	10>2 (Δ80%)	1>6	8.1>8.7 (Δ7.4%)

CRP=c-reactive protein; HAQ-DI=Health Assessment Questionnaire Disability Index.

disability; average pain score, ranging from 0 (no pain) to 10 (worst pain); fatigue index, which ranges from 0 to 10, with higher scores indicating greater fatigue; psychological well-being score, which ranges from 0 to 7, with higher scores indicating greater well-being; and serum inflammatory markers (c-reactive protein [CRP] reported here). Overall trends in the results (see **TABLE**) indicated significant improvement in these outcomes, except CRP levels for patient B. Methotrexate has many reported adverse side effects; patient B developed mucositis after six months of treatment, which resulted in lower the dose of methotrexate (2 2.5 mg tablets weekly) with resolution of mucositis.

A 2017 systematic review of consensus guidelines from the European League Against Rheumatism (2016), the Canadian Pain Society (2012), and the Association of the Scientific Medical Societies in Germany (2012) demonstrated some consensus among use of amitriptyline, anticonvulsants (mostly gabapentin), and serotonin-norepinephrine reuptake inhibitors with differing opinions about treatment with cyclobenzaprine, selective serotonin reuptake inhibitors, tramadol, and NSAIDs.[2] No class of disease-modifying antirheumatic drugs were recommended by these societies for treatment, including methotrexate. EBP

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Is naltrexone an effective treatment for adults with alcohol use disorder?

EVIDENCE-BASED ANSWER

Oral naltrexone 50 mg may reduce return to any drinking, heavy drinking, and number of heavy drinking days in adults with alcohol use disorder who go through a detoxification period (SOR: **B**, systematic review of randomized controlled trials [RCTs]) but not in adults who are currently drinking or have not gone through detox (SOR: **B**, systematic review of RCTs). Intramuscular naltrexone may only reduce the number of heavy drinking days per month (SOR: **B**, systematic review of RCTs). Naltrexone should be offered to patients with moderate-to-severe alcohol use disorder who have a goal of reducing alcohol consumption or achieving abstinence (SOR: **C**, practice guideline).

DOI 10.1097/EBP.0000000000001065

A 2014 systematic review and meta-analysis of 122 randomized controlled trials (RCTs) and one cohort study (N=22,803) analyzed adults with alcohol use disorder, examining the benefits and harms of pharmacotherapy in outpatient settings.[1] A subanalysis of 53 trials (N=9,140) examined oral naltrexone 50 to 100 mg daily and intramuscular naltrexone 380 mg monthly compared with control (psychosocial interventions). Participants who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for alcohol dependence or DSM-V criteria for moderate-to-severe alcohol use disorder were included. Most studies enrolled patients after detoxification or required at least a three-day period of sobriety, and all participants received treatment at outpatient specialty clinics with median follow-up of 12 weeks. Outcomes included return to any drinking, return to heavy drinking, and the number of heavy drinking days (>4 drinks per day for women; >5 for men) per month. Results were pooled and standardized into difference (risk difference) and weighted mean difference to account for heterogeneity among scoring measures. When compared with usual care, only oral naltrexone 50 mg significantly reduced return to drinking and return to heavy drinking (see **TABLE**). However, the effect size for 50 mg naltrexone was small with a higher number needed to treat. All three treatments significantly reduced the number of heavy drinking days per month compared with control (see **TABLE**). Additionally, dizziness, nausea, and vomiting were adverse events that occurred significantly more in treatment groups compared with usual care (see **TABLE**).

A 2017 network meta-analysis of 32 RCTs (N=6,036) assessed the efficacy of oral medications for the treatment of alcohol use disorder in adults.[2] This review included eight studies that were excluded from the above review. This network meta-analysis focused on nonabstinent patients, including patients with fewer than five days' abstinence before the beginning of the study and excluding studies when longer abstinence or detoxification was an explicit inclusion criterion. A subanalysis of 14 trials (n=850) specifically examined oral naltrexone (median dose 50 mg). Included participants were diagnosed with alcohol dependence or alcohol use disorder (criteria not specified). Outcomes measured included total alcohol consumption and the number of heavy drinking days per month measured at 8 to 36-week follow-up; median study duration was 12 weeks. Results were pooled and standardized into standard mean differences (SMDs) to account for heterogeneity. Compared with placebo, oral naltrexone had no significant treatment effect on total alcohol consumption (5 RCTs, N=793; SMD –0.11; 95% CI, –0.40 to 0.18) or heavy drinking days per month (8 RCTs, N=977; SMD –0.03; 95% CI, –0.21 to 0.16). Additionally, patients treated with naltrexone had a significant increase in adverse events (odds ratio, 2.21; 95% CI, 1.36–3.59) compared with control.

The 2018 American Psychiatric Association (APA) evidence-based practice guidelines recommended that naltrexone or acamprosate be offered to patients with moderate-to-severe alcohol use disorder who have a goal of reducing alcohol consumption or achieving abstinence, who prefer pharmacotherapy or have not responded to nonpharmacological treatments alone, and who have no contraindications to the use of these medications (moderate-strength recommendation).[3] The APA also recommended that naltrexone not be used by patients who have acute hepatitis or hepatic failure (low-strength recommendation) or by individuals who use opioids or who have an anticipated need for opioids (low-strength recommendation). EBP

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The authors declare no conflicts of interest.

TABLE. Outcomes and adverse events of naltrexone therapy started after alcohol detoxification[1]

	# RCTs	# Patients	NNT	Results (95% CI)
Return to any drinking				
Oral 50 mg	16	2,347	20	RD –0.05 (–0.10 to –0.002)
Oral 100 mg	3	946	NA	RD –0.03 (–0.08 to 0.02)
IM 380 mg	2	939	NA	RD –0.04 (–0.10 to 0.03)
Return to heavy drinking				
Oral 50 mg	19	2,875	12	RD –0.09 (–0.13 to –0.04)
Oral 100 mg	2	858	NA	RD –0.05 (–0.11 to 0.01)
IM 380 mg	2	615	NA	RD –0.01 (–0.14 to 0.13)
Heavy drinking days				
Oral 50 mg	6	521	NA	WMD –4.1 (–7.6 to –0.61)
Oral 100 mg	2	423	NA	WMD –3.1 (–5.8 to –0.3)
IM 380 mg	2	926	NA NNH	WMD –4.6 (–8.5 to –0.56)
Adverse events				
Dizziness	13	2,675	16	RD 0.06 (0.04 to 0.09)
Nausea	24	4,655	9	RD 0.11 (0.08 to 0.15)
Vomiting	9	2,438	24	RD 0.04 (0.02 to 0.06)

NA entry for NNT indicates that the RD (95% CI) was not statistically significant or that the effect measure was not one that allows for direct calculation of NNT (eg, WMD).
IM=Intramuscular; NA = not applicable; NNT=number needed to treat; NNH=number needed to harm; RCT=randomized controlled trial; RD=risk difference; WMD=weighted mean difference in days.

References

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