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EVIDENCE-BASED PRACTICE

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Family Physicians Inquiries Network

FPIN envisions a primary care workforce that thinks critically, communicates expertly, and utilizes the best current evidence to improve the health of patients.

Exporting ADHD

How do we define an illness? For the most part, mixing a pathology with a clinical syndrome works pretty well (pneumococcal pneumonia, HIV AIDs, *Clostridium difficile*–associated diarrhea, thrombotic stroke). But this is not quite as rigorous as it sounds, because what constitutes a clinical syndrome is always open to some debate and may be bound up in local cultural norms. I recently had a patient who complained of knee fullness, always followed by sharp pain over the medial malleolus, which was then followed by a deep ache in the thigh. Is that a clinical syndrome?

So I was fascinated to come across an article about the rising rates of attention deficit hyperactivity disorder (ADHD) around the world.[1] ADHD is a syndrome pretty well accepted in the United States. But until recently, the syndrome was not much recognized outside our borders. The authors noted that until the 1990s, the United States consumed 90% of the world's Ritalin®; now that figure is less than 75%. Australia, Brazil, China, Germany, Israel, the Netherlands, Norway, and the United Kingdom are now consuming more of the medication than before.

How did we export our syndrome, or more precisely, our concept of this syndrome? The authors pointed to multiple forces. The makers of ADHD drugs invested to "develop" these markets. The American concept that there are biological underpinnings to psychiatric distress was spreading. The Internet provided a platform for the rapid diffusion of both industry advertising and American medical concepts. The web also made available checklists that folks could use to diagnose themselves. Lastly, advocacy groups (working through the Internet and often supported by industry) spread awareness about and shaped policy around the syndrome.

In some countries (especially France), other factors slowed the spread of Ritalin prescribing: fears about stimulant safety or about stigmatizing kids with a label, laws stating only child psychiatrists could treat mental illness in kids, and a general resistance to using psychoactive medications on anyone.

Clearly the process of accepting any new clinical syndrome as legitimate is … untidy. But I think if we want to claim to be evidence-based physicians, we need to pay some attention to how that sausage is made.

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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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What are the risks and benefits of discontinuing bisphosphonate therapy?

EVIDENCE-BASED ANSWER

In postmenopausal women with osteopenia or osteoporosis, discontinuation of zoledronic acid (at 3 years) or alendronate (at 5 years) increases the risk of vertebral fractures, but not nonvertebral fractures (SOR: **B**, single RCT for each medication). However, women with a femoral neck T-score less than –2.5 after 5 years of alendronate have an increased risk of nonvertebral fracture when alendronate is discontinued (SOR: **B**, single RCT). Lower hip T-score (–2.3 to –4.2) and older age are associated with increased fracture risk during bisphosphonate holiday (SOR: **B**, single RCT).

Evidence summary

A 2012 RCT randomized postmenopausal women with osteoporosis (mean age 75.5 years) previously treated with an annual infusion of zoledronic acid 5 mg for 3 years to receive zoledronic acid for 3 additional years or placebo.[1]

Women who continued zoledronic acid had a lower risk of vertebral fracture measured by spine radiograph versus women who discontinued treatment (3.0% vs 6.2%; odds ratio 0.51; 95% CI, 0.26–0.95; number needed to treat [NNT]=31). No difference was noted in nonvertebral fractures, hip fractures, or adverse events between groups. No cases of atypical femoral fracture occurred in either group, whereas 1 case of osteonecrosis of the jaw was reported in the zoledronic acid group.[1]

Another RCT from 2006 evaluated the effect of bisphosphonate discontinuation among 1,099 postmenopausal women with osteopenia or osteoporosis who had previously received 5 years of alendronate.[2] Alendronate users were randomized to receive 5 more years of alendronate 5 to 10 mg/d or placebo.

Women who continued alendronate experienced less self-reported vertebral fractures (confirmed by a participant's physician) compared with women who discontinued (2.4% vs 5.3%; risk ratio [RR] 0.45; 95% CI, 0.24–0.85; NNT=34). No difference was noted in nonvertebral fractures (19.0% and 18.9%).[2]

A post hoc analysis of this RCT examined the effect of alendronate discontinuation on fracture in a subgroup of women without a history of vertebral fracture and whose femoral neck T-score was –2.5 or less after 5 years of alendronate.[3] Continuing alendronate 5 to 10 mg/d for 10 years instead of stopping after 5 years decreased the risk of nonvertebral fracture in women with femoral neck T-score less than –2.5 (RR 0.5; 95% CI, 0.26–0.96), but not if the T-score was more than –2.0.

Another post hoc analysis of 437 participants from the same RCT who received placebo during the extension phase examined potential risk factors for fracture after alendronate discontinuation, including patient age, bone mineral density (BMD), and bone turnover markers (BTM).[4]

The risk of fracture in the lowest tertile of baseline total hip BMD (baseline hip T-score –2.3 to –4.2) was 87% higher compared with the other 2 tertiles (hazard ratio [HR] 1.9; 95% CI, 1.2–2.9). Older age was also associated with higher risk of fracture (HR 1.5; 95% CI, 1.3–1.9 per 5-year increase in age). Overall, 94 of 437 (22%) women had a fracture during the alendronate holiday.[4] EBP

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We hope you enjoy our fall double issue and the new cover of *Evidence-Based Practice* this year! For questions, email us at **EBP@fpin.org.**

It's never too late; Steroids for late preterm delivery

Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al; NICHD Maternal–Fetal Medicine Units Network. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med*. 2016; 374(14):1311–1320.

This double-blind, randomized, placebo-controlled trial of 2,381 pregnant women investigated whether the use of antenatal corticosteroids in women at risk for late preterm delivery decreases the risk of neonatal morbidity. Women with a gestational age between 34 and 36 weeks, with a high probability of late preterm delivery, received 2 intramuscular injections 24 hours apart of either 12 mg betamethasone or placebo.

Primary outcomes included the need for respiratory support within 72 hours of birth (defined as use of continuous positive airway pressure, high-flow nasal cannula for at least 2 hours, supplemental oxygen of ≥30% for ≥4 hours, extracorporeal membrane oxygenation, or mechanical ventilation), stillbirth, or neonatal death within 72 hours of delivery.

The primary outcome occurred less in the treatment group compared with the placebo group (11.6% vs 14.4%; relative risk [RR] 0.80; 95% CI, 0.66–0.97; number needed to treat=35). Rates of transient tachypnea of the newborn (RR 0.68; 95% CI, 0.53–0.87), bronchopulmonary dysplasia (RR 0.22; 95% CI, 0.02–0.92), resuscitation at birth (RR 0.78; 95% CI, 0.66–0.92), and surfactant use (RR 0.59; 95% CI, 0.37–0.96) were also significantly lower in the treatment group. Although the risk of chorioamnionitis or neonatal sepsis was not increased among infants who received betamethasone, they had a higher risk of hypoglycemia (absolute risk increase 9%; RR 1.6; 95% CI, 1.37–1.87) that was not associated with longer hospital stays.

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	Yes	Clinically meaningful	Yes

Bottom line: Corticosteroids can reduce respiratory complications in late preterm infants without significant neonatal or maternal complications.

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A stone's throw away from treatment: Nifedipine or tamsulosin for kidney stone therapy?

Pickard R, Starr K, MacLennan G, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015; 386(9991):341–349.

This placebo-controlled RCT compared medical expulsion therapy with tamsulosin or nifedipine to each other or placebo for patients with a kidney stone 10 mm or less in diameter. Patients (N=1,167) were randomized in a 1:1:1 fashion to receive tamsulosin 0.4 mg (n=391), nifedipine 30 mg (n=387), or placebo (n=389) daily until kidney stone passage or up to 4 weeks.

The primary outcome was spontaneous stone passage, as defined by the lack of need for additional intervention at 4 weeks. The study was powered to detect a 10% difference of stone passage between tamsulosin and nifedipine. Secondary outcomes included patient-reported analgesic use and pain, time to stone passage, and adverse event reporting.

Spontaneous stone passage did not differ between medical expulsion therapy and placebo (odds ratio [OR] 1.06; 95% CI, 0.7–1.6). Additionally, no difference was noted in spontaneous stone passage when comparing tamsulosin versus nifedipine (OR 1.06; 95% CI, 0.7–1.5). No differences were found between any of the secondary outcomes.

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	Yes	Clinically meaningful	Yes

Bottom line: Treatment with tamsulosin or nifedipine is not useful for increasing the chances of spontaneous stone passage in patients acutely presenting with kidney stones 10 mm or less in diameter. EBP

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We invite your questions and feedback.
Email us at **EBP@fpin.org.**

Should you discontinue beta-blockers in patients admitted for a CHF exacerbation currently taking a beta-blocker?

CASE

A 67-year-old man with a history of hypertension and heart failure presents to the emergency department with 3 days of progressively worsening dyspnea on exertion, mild nonproductive cough, increasing lower extremity edema, and orthopnea. ECG shows normal sinus rhythm with mild left ventricular hypertrophy, and chest radiography is significant for cardiomegaly with cephalization and bilateral pleural effusions. The intern inquires whether the patient's beta-blocker should be continued or withdrawn during this admission for an acute heart failure exacerbation.

Review of evidence

In a 2008 subanalysis of a larger heart failure study, the influence of beta-blocker continuation or withdrawal was evaluated in 1,537 patients who took beta-blockers and then were hospitalized with heart failure.[1] Of the patients hospitalized with new or worsening heart failure on beta-blockers prior to admission, 1,350 were continued on this therapy, 187 had beta-blockers discontinued for intolerance or contraindications, and 79 were eligible to continue but had the therapy withdrawn. All-cause mortality for patients was evaluated at 60 and 90 days. Analysis was adjusted for variables predictive of postdischarge mortality.

All-cause mortality was increased for patients who had beta-blocker therapy withdrawn compared with patients who continued their beta-blocker therapy (hazard ratio [HR] 2.3; 95% CI, 1.2–4.6). No difference was noted between the groups when all-cause mortality and rehospitalization were combined as outcomes (HR 1.11; 95% CI, 0.67–1.9).[1]

A 2009 post hoc analysis of data from an RCT (N=1,088), which initially evaluated the effects of different beta-blockers on chronic heart failure, examined the effectiveness of beta-blockers when withdrawn or reduced after hospitalization for decompensated heart failure.[2] Of the patients hospitalized for heart failure, 752 were maintained on beta-blockers (529 on the same dose while 162 had reduced dosing) and 61 had beta-blocker therapy withdrawn.

Mortality was evaluated at 58 months and showed a lower mortality risk in patients maintained on beta-blocker therapy whether or not the dose was reduced (HR 0.60; 95% CI, 0.33–0.94).[2]

A post hoc analysis of a cohort trial, which examined the effects of beta-blocker therapy before and after hospitalization, reviewed the mortality outcomes of 432 patients with heart failure who either continued or discontinued beta-blockers during hospitalization.[3] Patients who had beta-blockers discontinued during hospitalization did not restart after hospitalization. Of the patients hospitalized, 268 were on a beta-blocker prior to admission, and 263 were included in the analysis. Overall, 209 patients were discharged on beta-blockers, and 54 had their beta-blocker stopped or not continued at discharge.

Mortality and rehospitalization rates were reduced at 180 days postdischarge for patients continued on beta-blockers (OR 0.27; 95% CI, 0.10–0.71).[3]

The 2012 evidence-based *Canadian Cardiovascular Society Heart Failure Management Guidelines Update: Focus on Acute and Chronic Heart Failure* recommended continuation of chronic beta-blocker therapy for acute heart failure unless the patient has symptomatic bradycardia or hypotension (no grade provided).[4]

CASE WRAP-UP

Beta-blocker therapy during this patient's hospitalization for acute heart failure exacerbation should be continued unless contraindicated due to symptoms such as bradycardia or hypotension. EBP

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Are proton pump inhibitors (PPIs) more effective than H2 receptor agonists (H2RAs) for adults with gastroesophageal reflux disease (GERD)?

EVIDENCE-BASED ANSWER

Yes. PPIs are more effective than H2RAs for empiric treatment of adults with GERD symptoms. PPIs are also more effective than H2RAs in patients with GERD symptoms regardless of whether or not they have esophageal erosions on endoscopy (SOR: **B**, meta-analyses of RCTs).

A 2013 systematic review and meta-analysis of 19 RCTs (N=6,734) compared PPIs with H2RAs for the empiric treatment of GERD.[1] The trials enrolled adults with symptoms of heartburn (mean age 51 years, 54% male). PPIs included omeprazole (20 mg BID or 40 mg daily) or pantoprazole (20 or 40 mg daily) and were compared with the H2RAs cimetidine (300 or 400 mg QID), famotidine (20 mg BID or 40 mg daily), nizatidine (150 mg BID), or ranitidine (150 mg BID or 300 mg daily). Duration of treatment was 1 to 12 weeks. The primary outcome was rate of heartburn remission (defined as no more than 1 day per week with mild heartburn).

PPIs decreased the risk of persistent heartburn in patients with empirically treated GERD compared with H2RAs (7 trials, n=1,724; relative risk [RR] 0.66; 95% CI, 0.60–0.73). The quality of this evidence is limited by moderate heterogeneity.[1]

A 2013 systematic review and meta-analysis of 17 RCTs (N=6,072) compared PPIs with H2RAs for the treatment of nonerosive esophageal reflux disease (NERD).[2] Patients were adults (mean age 48 years, 42% male) with typical GERD symptoms and an endoscopically normal esophagus. PPIs included omeprazole (10 or 20 mg), esomeprazole (20 and 40 mg), lansoprazole (15 and 30 mg), rabeprazole (5, 10, or 20 mg), dexlansoprazole (30 or 60 mg), and pantoprazole (20 or 40 mg) and were compared with the H2RAs ranitidine (75, 150, or 300 mg), famotidine (20 mg), roxatidine (75 mg), or nizatidine (150 mg). Treatment courses ranged from 1 to 6 months.

PPIs increased rate of symptomatic relief (relief of heartburn or regurgitation) compared with H2RAs (7 trials, n=1,882; RR 1.6; 95% CI, 1.4–1.9). Although there was no statistically significant heterogeneity, the RCTs were at risk of bias (allocation and blinding methods were unclear).[2]

A 1997 systematic review and meta-analysis of 43 RCTs (N=7,635) compared the effectiveness of PPIs with H2RAs in adults with endoscopically proven moderate to severe erosive esophagitis (grade II, 62%; grade III, 32%; grade IV, 6.5%).[3] Patients were adults (mean age 51 years, 65% male). PPIs (omeprazole, lansoprazole, or pantoprazole) were compared with H2RAs (cimetidine, nizatidine, ranitidine, and famotidine) for 2 to 12 weeks. The outcomes included overall healing proportions and healing rate (percentage of patients healed per week).

PPIs increased healing proportion (87%; 95% CI, 79–88) versus H2RAs (52%; 95% CI, 47–57). PPIs increased healing rate (12%; 95% CI, 11–13) versus H2RAs (5.9%; 95% CI, 5.5–6.3). In a subgroup analysis, PPIs increased the percentage of patients who were heartburn free compared with H2RAs (16 trials, n=2,198; 77% vs 49%; $P<.0001$).[3]

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Does bicycling, in otherwise healthy men, increase the risk of erectile dysfunction?

EVIDENCE-BASED ANSWER

There is no association between bicycling and erectile dysfunction (ED), and no dose-response relationship (SOR: **B**, cross-sectional population studies).

A 2011 cross-sectional study of men in 5 Korean workplaces evaluated ED in 142 bicyclists (average age 44 years) and 83 noncyclists (average age 42 years) free of major medical, neurological, and urological disease.[1] Data were collected through a self-administered survey incorporating the International Index of Erectile Function-5 (IIEF-5)

TABLE

Association between cycling and self-reported erectile dysfunction in UK men[3]

Weekly cycling time (hours/week)	% Prevalence (cases/n)	Odds ratio (95% CI)
<3.75	9.8 (124/1,269)	Reference
3.75–5.75	7.2 (88/1,223)	0.75 (0.55–1.01)
5.76–8.5	7.6 (114/1,492)	0.79 (0.60–1.05)
>8.5	9.3 (115/1,243)	0.92 (0.69–1.23)

questionnaire, with ED defined as an IIEF-5 score less than 22. Cyclists were members of a bicycling club for at least 6 months, with noncyclists used as controls.

The difference in prevalence of ED in cyclists (46.1%) and noncyclists (55.4%) was not statistically significant (*P*=.071). A subanalysis of cycling hours and frequency versus prevalence of ED found no significant correlations.[1]

A 2011 cross-sectional study of healthy Korean men compared ED in 22 amateur bicyclists (cycling 30 minutes, ≥3 times a week for 1 year, average age 49 years) and 17 amateur marathon club members (average age 51 years) using the IIEF-5 survey.[2] ED was defined as an IIEF-5 score less than 22. The difference in prevalence of ED (50% in cyclists, 58.8% in marathoners) was not statistically significant (*P*=.748).

A 2014 cross-sectional study of 5,226 cyclists in the United Kingdom conducted via online survey compared the rate of self-reported ED, with weekly cycling time as a potential indicator of causality.[3] No association between cycling time and ED was identified after adjustment for age, body mass index (BMI), smoking, alcohol intake, hypertension, or other physical activity (see **TABLE**).

A 2001 cross-sectional study of 1,277 men (average age 55 years, BMI 27.4 kg/m^2) near Boston, Massachusetts evaluated prevalence of moderate to severe ED in noncyclists (n=1,164) versus moderate cyclists (<3 hours/week, n=90) and intense cyclists (≥3 hours/week, n=23).[4] Cycling hours were obtained via subject recall of the previous week, and ED was assessed through a self-administered questionnaire containing 9 items addressing erectile function. An algorithm was used to distinguish subjects who reported moderate to severe ED versus subjects with little or no ED, and an odds ratio was calculated for each group, adjusted for age, kcal expended per day, BMI, weight, smoking, depression, cancer, hypertension, and diabetes.

The incidence of ED in moderate cyclists and intense cyclists was not significantly different from that of noncyclists.[4]

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Does the presence of lower extremity edema affect outcomes of patients with lower extremity cellulitis?

EVIDENCE-BASED ANSWER

Edema in patients with cellulitis is associated with increased mortality by a year and triples the odds of recurrent cellulitis (SOR: **B**, cohort studies). Current guidelines recommend treatment of edema to prevent recurrent cellulitis (SOR: **C**, consensus guideline).

A 2007 retrospective cohort of 568 patients admitted into 2 general hospitals for cellulitis reviewed mortality associated with the presence of edema.[1] The data set was gathered between 2001 and 2003 to review cellulitis outcomes in patients treated with flucloxacillin alone (20%), flucloxacillin with benzylpenicillin (60%), or benzylpenicillin alone (12%). Patients were 50 years old or older and many had comorbidities such as diabetes mellitus (16%), obesity (57%), and lymphedema (18%), while 39% of the cohort had characteristics that identified them as high risk for mortality

defined as prior coronary artery bypass graft, past myocardial infarction, cancer, penetrating injury, bed bound or immobile, and medications leading to edema or salt retention.

Lower leg edema was a negative predictor for survival at 1 year (odds ratio [OR] 0.47; 95% CI, 0.31–0.81). The most significant confounder—antibiotic used—was controlled for and authors excluded variables for which more than 10% of data was missing. The study did not provide diagnostic criteria for edema.[1]

A 2006 retrospective cohort of 171 patients admitted with ascending cellulitis to 2 general hospitals evaluated the relationship of edema to subsequent recurrent lower leg cellulitis.[2] Diagnostic criteria of ascending cellulitis included malaise, shivering, or fever plus localized redness, warmth, and swelling not due to another cause (eg, deep venous thrombosis, penetrating injury, or bilateral lymphedema). Patient and primary care physician surveys were collected on 143 of the patients.

Persistent edema was associated with more recurrent cellulitis (OR 3.2; 95% CI, 1.7–5.9). Additionally, 37% of the surveyed patients noted development of edema as a result of the cellulitis. Limitations of the study include lack of demographic data and incomplete data collection on the primary cohort.[2]

A 2014 evidence-based guideline from the Infectious Diseases Society of America reviewed management and risk factors for cellulitis.[3] Based on the strong association of edema with recurrent cellulitis, the guideline recommended reduction of edema through elevation, compression, and diuretics if indicated to prevent recurrences, while acknowledging lack of direct evidence of benefit. This was a strong recommendation ("benefit clearly outweighs risk") with moderate evidence ("weak RCTs or strong evidence from observational studies").

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What is the best imaging strategy for diagnosing a painless scrotal mass?

EVIDENCE-BASED ANSWER

Ultrasonography is a useful first step in imaging a painless scrotal mass. Ultrasonography is 98% to 100% sensitive for detecting malignant intratesticular lesions requiring surgery, but the specificity is unknown (SOR: **C**, low-quality observational studies). Magnetic resonance imaging (MRI) is an appropriate second step for identifying malignancy when ultrasonography is equivocal (SOR: **C**, case series).

A single-center case series from 1991 to 2007 examined 383 pediatric patients who presented with scrotal abnormalities; the most common complaint (75%) was painless mass/fullness.[1] Of those patients, 12 had a histologically proven intratesticular neoplasm, and ultrasound was able to correctly identify benign masses versus malignant masses in all 12 (100% accuracy). Additionally, when coupled with hormonal testing, ultrasound accurately predicted specific histologies such as germ cell or sex cord tumors.

A 2004 case series of 230 patients 15 to 45 years old with acute and subacute scrotal enlargement and penile masses were evaluated with radiologic imaging for diagnosis.[2] All of the patients were evaluated by ultrasound first, and patients with equivocal findings were then assessed with MRI. Of the 210 patients with scrotal mass, 18% (37 patients) had MRI performed. Clinical follow-up or surgical exploration determined the final diagnosis.

Ultrasound correctly diagnosed epididymo-orchitis in 95 of 97 cases (98% sensitive) and was 100% accurate for identifying benign lesions (varicoceles and hydroceles). Of the patients who underwent MRI due to equivocal ultrasound findings, 23 had testicular cancer, and the MRI correctly identified 100% of these cases.[2]

A 10-year multicenter case series from 1980 to 1991 of 71 pediatric patients between the ages of 1 day to 16 years with history of painless scrotal mass (excluding patients with previously known hernia, varicocele, and hydrocele) examined the role of ultrasound in evaluating painless scrotal masses and surgical decision-making.[3] Ultrasound correctly identified (based on surgery or clinical follow-up)

all 45 patients for whom surgical management was indicated (45 cases, or 63% of the total cases), and also was able to identify pathognomonic findings for nonsurgical pathologies: epididymal cysts, spermatocele, or neonatal torsion/necrosis (26 cases, or 37% of the total cases).

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

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Are azapirones more effective than placebo in treating panic disorder among adults?

EVIDENCE-BASED ANSWER

Azapirones (buspirone) are probably not more effective than placebo in decreasing panic attacks and anxiety symptoms in adults with panic disorder. In addition, azapirones are less well tolerated than placebo (SOR: **B**, systematic review of low-quality RCTs and single RCT).

A 2014 systematic review analyzed 3 RCTs comparing the oral azapirone, buspirone (mean delivered dose 29.5–61 mg/d) with placebo for the treatment of adults (N=170) with panic disorder.[1] Studies in which participants received other treatments, including psychotherapy, were excluded. The duration of the intervention was 8 weeks. Results were not pooled because of a use of different symptom scales and lack of reporting of standard deviations.

One study (n=44) showed no significant difference in the number of panic attacks between buspirone and placebo. A second trial (n=75) evaluated the frequency of panic attacks in the preceding 2 weeks at baseline and then at 2-week intervals. At week 8, the buspirone group showed a mean decrease of 3.8 panic attacks over the preceding 2-week period versus baseline (95% CI, –5.6 to –2.0). The third analyzed trial (n=23) evaluated the frequency of panic attacks per week at baseline and then weekly. At week 8 of therapy, the buspirone group had a median decrease of 1 panic attack per week versus baseline (statistical analysis not reported). Over the study period, the risk for study dropout increased with buspirone (RR 2.1; 95% CI, 1.1–4.1), suggesting that buspirone was less well tolerated than placebo. Secondary efficacy outcomes measuring agoraphobia, anxiety, and depression symptoms on various scales were not statistically different between groups. The included studies had significant limitations, including insufficient reporting of allocation concealment and sequence generation, with high rates of attrition and small sample sizes.[1]

Another RCT not included in the systematic review above, due to use of cognitive behavioral therapy (CBT), randomized 77 patients with panic disorder to CBT plus placebo or CBT plus buspirone up to 60 mg daily (mean delivered dose 30 mg daily).[2] A 2-week trial of placebo occurred prior to randomization, and only placebo nonresponders were subsequently randomized. Of note, 15% of recruited patients had a 50% improvement in symptoms with placebo. Only 41 patients were followed to completion of the study, for a 37% dropout rate. The primary outcome was change on the Phobia, Panic, and Generalized Anxiety (PPGA) scale, with 3 subdomains of agoraphobia, generalized anxiety, and number of spontaneous panic attacks, each rated 0 to 8, with higher scores correlating to more symptoms.

From baseline to 16 weeks, CBT plus buspirone resulted in a slightly greater reduction in symptoms of generalized anxiety than CBT plus placebo (difference in mean change on PPGA generalized anxiety scale of –1.5; $P<.05$), but the difference was not sustained at 1 year. The subdomains of agoraphobia and number of panic attacks did not differ between groups. Multiple other secondary outcome measures of general improvement, agoraphobia, anxiety, and depression did not show any between-group differences.[2]

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How does regional anesthesia (epidural or combined spinal-epidural) affect childbirth outcomes?

EVIDENCE-BASED ANSWER

Epidural and combined spinal-epidural (CSE) analgesia increase the risk for instrumental vaginal delivery, maternal hypotension, prolonged second stage of labor, and need for oxytocin augmentation, without increasing the overall risk of cesarean section (SOR: **A**, systemic review of RCTs). They have no immediate adverse effects on neonatal outcomes as determined by low Apgar scores or neonatal intensive care unit (NICU) admission (SOR: **A**, systematic review of RCTs). There is less risk of instrumental delivery with CSE than traditional epidural (SOR: **A**, systemic review of RCTs).

In 2011, a meta-analysis analyzing 38 RCTs (N=9,658) compared the effects and safety of regional epidural analgesia on the mother and neonate.[1] Patients were laboring women, regardless of parity (induced or spontaneous). This study specifically compared outcomes with epidural or CSE and nonepidural methods of analgesia (number of participants per intervention not delineated).

Regional forms of analgesia were associated with increased risk of instrumental delivery (24 trials, n=7,935; relative risk [RR] 1.4; 95% CI, 1.3–1.6, number needed to treat=20), longer second stage of labor (13 trials, n=4,233; mean difference 14 minutes; 95% CI, 6.7–21), need for augmentation with oxytocin (13 trials, n=5,815; RR 1.2; 95% CI, 1.0–1.4), maternal hypotension (8 trials, n=2,789; RR 18; 95% CI, 5.1–65), and cesarean section for fetal distress (11 trials, n=4,816; RR 1.4; 95% CI, 1.0–2.0). However, no significant difference was noted in the overall risk for of cesarean delivery (27 trials, n=8,417; RR 1.1; 95% CI, 1–1.3).[1]

For neonates, there was no increased risk of low Apgar scores (<7) at 5 minutes (18 trials, n=6,898; RR 0.80; 95% CI, 0.54–1.2) and no change in risk of NICU admission (7 trials, n=3,125, RR 1.2; 95% CI, 0.94–1.5). There was a reduced risk of acidosis as defined by cord blood arterial pH <7.2 (7 trials, n=3,643; RR 0.80; 95% CI, 0.68–0.94). Of note, significant heterogeneity was found with regards to length of second stage of labor, oxytocin augmentation, and maternal hypotension.[1]

A 2012 meta-analysis of 27 RCTs (N=3,274, no coinciding trials with the above RCT) compared childbirth outcomes between CSE and tradition epidural analgesia.[2] Patients were laboring women, regardless of parity, who received either form of regional analgesia during the first stage of labor.

Rates of instrumental delivery were decreased with CSE versus traditional epidural anesthesia (6 trials, n=1,015; RR 0.81; 95% CI, 0.67–0.97). No statistical difference was found between CSE and traditional epidural for labor augmentation, the rate of caesarean birth, neonatal Apgar scores, or umbilical artery pH.[2]

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Does self-monitoring blood glucose improve outcomes in patients with type 2 diabetes not taking insulin?

EVIDENCE-BASED ANSWER

In patients with type 2 diabetes (T2DM) not requiring insulin, self-monitoring of blood glucose (SMBG) has inconsistent effects on patient-oriented outcomes such as quality of life (QOL), hypoglycemia, and patient satisfaction. The effect of SMBG is also inconsistent on all-cause mortality and diabetic complications. SMBG is associated with small but clinically insignificant reductions in hemoglobin A1C (HbA1C) (SOR: **C**, meta-analysis of RCTs with disease-oriented outcomes).

A 2012 meta-analysis of 9 RCTs (N=2,324) compared SMBG (frequency 2x/wk to 6x/d) versus no monitoring in patients with T2DM treated with oral agents or lifestyle modification.[1] The primary outcome was HbA1C at 3, 6, and 12 months and secondary outcomes were QOL and patient satisfaction.

The SMBG groups showed statistically significant reductions in HbA1C, but the clinical effect was small and waned over time (at 6 months, –0.3; 95% CI, –0.4 to –0.1; and at 12 months –0.1; 95% CI, –0.3 to 0.04). Five trials reported on

patient satisfaction or QOL. One trial demonstrated a small but statistically significant decrease in depression subscale QOL scores (range of scores 0–18) favoring SMBG (–0.83 vs –0.26; *P*=.03), while another study reported a 6% increase in depression subscale scores on the same scale in the SMBG group at 12 months (*P*=.01). Of the 3 trials that measured QOL with a survey, only 1 found a small but statistically significant difference of –0.1 (range of scores 1–3) favoring the control group (95% CI, –0.127 to –0.017). None of the 5 trials found differences in patient satisfaction.[1]

A 2012 meta-analysis of 6 RCTs compared SMBG (frequency not specified) with no SMBG for 2,552 patients with T2DM managed by lifestyle modification or adjustment of oral agents.[2] All 6 trials were included in the meta-analysis above, but the other 3 trials in that meta-analysis were outside of the search dates of 2000 to 2010. Mean age was 60.1 years, baseline HbA1C was 8.3%, and 54% were male.

HbA1C reduction in the SMBG group was statistically significant but not clinically meaningful when the data were adjusted for age, sex, and duration of diabetes (at 3 months –2.0; 95% CI, –3.2 to –0.9; at 6 months –2.7; 95% CI, –3.9 to –1.6; and at 12 months –2.5; 95% CI, –4.1 to –0.9).[2]

A 2010 systematic review of 26 RCTs (N=5,373) compared HbA1C in patients with T2DM on oral agents and/or basal insulin using SMBG versus no monitoring over 3 to 30 months.[3] Ten RCTs comparing SMBG with no SMBG (N=1,148) were pooled in a meta-analysis. Mean age was 57.5 years and mean HbA1C was 8.9%. SMBG frequency varied from no regimen, twice every other day, to as frequently as 6 times a day.

The SMBG groups had a statistically significant but clinically insignificant reduction in HbA1C (–0.21%; 95% CI, –0.31 to –0.10) compared with no SMBG. Six of the RCTs (n=2,202) compared hypoglycemic events between SMBG and no SMBG groups. The studies could not be pooled for meta-analysis. One study found decreased hypoglycemic events with SMBG, 1 study found an increase, 2 studies found no difference, and 2 studies did not comment on the results. Seven of the RCTs (n=1,288) compared QOL between SMBG and no SMBG groups: 3 trials found increased anxiety and depression symptoms with SMBG, 1 trial showed decreased depression symptoms with SMBG, 2 found no difference, and 1 did not comment. None of the RCTs studied diabetes-related morbidity or all-cause mortality, but the authors noted 1 observational study (n=1,286) reported no change in all-cause mortality. Another observational study (n=3,268) suggested a decrease in both diabetes-related morbidity and all-cause mortality with SMBG. The authors admitted that these observational studies were potentially skewed by confounding variables.[3]

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Are serial ECGs useful in the diagnosis of myocardial infarction?

EVIDENCE-BASED ANSWER

Timely serial electrocardiograms (ECGs) in patients presenting with chest pain can aid in the diagnosis of myocardial infarction (MI). Most acute MIs are diagnosed with the first ECG, but subsequent ECGs completed 9 to 30 minutes after the initial ECG can identify 15% to 20% of initially undetected MIs (SOR: **B**, prospective and retrospective cohort studies). ECGs should be performed every 15 to 30 minutes during the first hour after presentation then every 3 to 6 hours (SOR: **C**, consensus guidelines).

A 1998 prospective observational study of 1,000 patients who presented to the emergency department (ED) with chest pain, and who were then admitted for concern of coronary ischemia, evaluated the usefulness of serial ECGs compared with initial ECG in detecting MI.[1] Of patients admitted, 61% were male, 80% were white, the average age was 56 years, and 42% had a history of coronary artery disease. Each patient had an initial ECG, and then additional ECGs were performed every 20 minutes while in the ED.

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Of the 204 patients with acute MI (defined as creatine kinase elevation, new Q wave, or death within 24 hours), the initial ECG was diagnostic of an acute MI in 113 patients (55.4%); further ECGs did not provide additional information in these patients. Serial ECGs detected acute MIs in an additional 16% of patients. The sensitivity of initial ECG and serial ECGs was 55% (95% CI, 49–62) and 68% (95% CI, 62–75), respectively. The specificity of both the initial ECG and serial ECG was about 95%.[1]

A 1996 retrospective cohort study reviewed 114 patients with a discharge diagnosis of acute MI to determine the proportion of patients with a non-ST-segment elevation MI on their initial ECG who developed ST-segment elevations during their hospital course.[2] ECGs were obtained on arrival to the ED and every 8 hours for the first 48 hours. Patients were divided into 3 groups based on the method of diagnosis: Group A (n=20 had ST-segment elevations on their initial ECG; group B (n=19) had initial nondiagnostic ECGs and subsequently developed ST-segment elevations while hospitalized; and group C (n=75) never developed ST-segment elevations, but rather were diagnosed by serial enzymes. The average ages of groups A, B, and C were 71.1, 70.5, and 73.3 years, respectively. The average number of cardiac risk factors in groups A, B and C were 2.35, 2.74, and 2.35, respectively. Males constituted 55% of group A, 79% of group B, and 73% of group C.

There were 94 diagnosed MIs. Of those, 20% (19 patients) had initial nondiagnostic ECGs and subsequently developed ECG changes that met thrombolytic criteria.[2]

A 2012 retrospective cohort study evaluated 325 prehospital ST-segment elevation MIs (STEMIs) identified by paramedics to determine the utility of serial ECGs compared with initial ECG in the diagnosis of STEMI.[3] The median age of the patients was 65 years.

Of the 325 STEMIs, 275 (85%) were diagnosed on their first ECG, 30 (9%) were diagnosed on the second ECG, and 20 (6%) on the third ECG. The 3 ECGs were performed 10 minutes apart. For STEMIs identified on the second and third ECG, 90% were identified within 25 minutes after the first ECG.[3]

According to 2014 American Heart Association/American College of Cardiology guidelines on the management of patients with non-ST-segment elevation acute coronary syndromes (ACS), patients with a high clinical suspicion for ACS with continued symptoms should undergo serial ECGs at 15- to 30-minute intervals during the first hour even if their initial ECG is normal.[4] In patients with intermediate or high clinical suspicion for ACS, additional troponin levels and serial ECGs should be performed after 6 hours of symptom onset. If patients present to the ED with chest pain and their initial ECG and troponin levels are normal, it is reasonable to observe them in a chest pain unit and perform serial ECGs and troponins at 3- to 6-hour intervals.

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What is the best regimen to prevent exercise-induced bronchoconstriction in a child with underlying asthma?

EVIDENCE-BASED ANSWER

Short- and long-acting inhaled beta$_2$-agonists are better than placebo for protecting against a decrease in forced expiratory volume at 1 second (FEV1) during exercise-induced bronchoconstriction (EIB) (SOR: **B**, meta-analysis with heterogeneity). Daily montelukast with or without inhaled budesonide is better than budesonide alone or budesonide with inhaled formoterol for protecting against a decrease in FEV1 during EIB (SOR: **B**, single RCT).

A 2013 systematic review compared pretreatment with inhaled beta$_2$-agonists versus placebo for change in FEV1 in children and adults with EIB (53 trials, N=1,139).[1] The authors

TABLE

Percent change in maximum percentage decrease in FEV1 after exercise from baseline to after 4 weeks treatment[2]

Group	Mean percent change in decrease of FEV1	Standard error (±)	*P* value
Budesonide plus formoterol	–24.4	2.59	<.001
Budesonide plus montelukast	–52.1	4.6	<.001
Montelukast	–53.5	3.62	<.001
Budesonide	–31.5	4.11	<.001
Placebo	9.4	1.77	.36

included only randomized, double-blind placebo-controlled trials, of which 48 used a crossover design and the remaining 5 used a parallel study design. A subgroup analysis of children only compared placebo with a single prophylactic dose of an inhaled beta$_2$-agonist (32 trials, n=342).

Albuterol was the most common short-acting beta$_2$-agonist (SABA), with doses ranging from 180 to 400 mcg and given within 1 hour before exercise. Salmeterol, dosed at 25 or 50 mcg, was the most common long-acting beta$_2$-agonist (LABA) given within 12 hours before exercise.[1]

Compared with patients using inhaled beta$_2$-agonists, patients in the placebo groups had greater declines in FEV1 (mean difference [MD] –15.3%; 95% CI, –18.9 to –11.8) with exercise. Pediatric trials had a high degree of heterogeneity (I^2 = 80%).[1]

A 2008 double-blind RCT compared different asthma treatment regimens with each other and with placebo for preventing EIB in children with asthma (N=100).[2] Treatment regimens included 200 mcg budesonide daily, 200 mcg budesonide plus 5 or 10 mg montelukast daily at bedtime, 100 mcg budesonide with 4.5 mcg formoterol twice daily, or 5 to 10 mg montelukast given daily.

After 4 weeks, all active treatment groups had significantly reduced FEV1 after exercise compared with baseline and compared with placebo (*P*<.001) (see **TABLE**). The greatest changes occurred with budesonide plus montelukast and montelukast alone, and both treatments were significantly better than budesonide plus formoterol (*P*<.001) and budesonide alone (*P*=.002). No significant difference was found between budesonide plus montelukast and montelukast alone (*P*=.9).[2]

A 2010 evidence-based practice parameter stated that inhaled beta$_2$-agonists were most effective for short-term protection against EIB and for recovery of FEV1 after a decrease due to exercise (SOR A, "evidence from a systematic review of RCTs").[3] Addition of leukotriene inhibitors or mast cell stabilizers as intermittent or daily therapy was recommended to reduce symptoms of EIB, but not to reverse airway obstruction (SOR A). Inhaled corticosteroid therapy was also mentioned as a way to decrease the frequency and severity of EIB (SOR A).

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Are any beta-blockers less likely to cause erectile dysfunction?

EVIDENCE-BASED ANSWER

Compared with other beta-blockers, nebivolol does not appear to negatively affect erectile function in men while still significantly lowering heart rate (HR) and blood pressure (BP) (SOR: **B**, single RCT and observational studies).

A 2005 randomized double-blind study including a total of 131 patients (mean age 47 years) with newly diagnosed hypertension compared the effects of nebivolol and atenolol with and without chlorthalidone on sexual function.[1] All patients were married and had not previously experienced erectile dysfunction. After a 4-week placebo run-in, patients were randomized to receive 12 weeks of therapy with nebivolol 5 mg/d (n=43), atenolol 50 mg/d (n=44), or atenolol 50 mg/d + chlorthalidone 12.5 mg/d (n=44). Erectile function (instances of successful intercourse/month), BP, and HR were assessed by means of a questionnaire at the end of

the placebo run-in period and at the end of the double-blind treatment period.

At the end of the 12-week double-blind treatment period, the mean number of episodes of satisfactory sexual intercourse per month was significantly decreased from baseline in the groups receiving atenolol (7.0 episodes decreased to 3.7; *P*<.01) and atenolol plus chlorthalidone (6.4 decreased to 2.8; *P*<.01). In contrast, the number of episodes in the nebivolol group remained nearly the same (6.4 decreased to 6.0) and significantly more than after atenolol plus chlorthalidone (*P*<.01). BP and HR were significantly decreased from baseline in all treatment groups. BP was reduced by 25.8/8.5 mmHg with atenolol, 24.7/11 mmHg with nebivolol, and 24.6/10.8 mmHg with atenolol plus chlorthalidone. The differences in systolic BP were not statistically significant for the 3 treatment groups, whereas the differences in diastolic BP between nebivolol and atenolol as well as between atenolol and atenolol plus chlorthalidone were statistically significant (*P*=.003 and *P*=.001, respectively). HR was reduced by 16.2 beats/min with atenolol, 12.3 beats/min with nebivolol, and 14.8 beats/min with atenolol plus chlorthalidone. Atenolol and atenolol plus chlorthalidone reduced HR significantly more than nebivolol (*P*=.0003 and *P*=.001, respectively).[1]

A 2010 cross-sectional study of 1,007 hypertensive men (mean age 58 years) evaluated the prevalence of erectile dysfunction (ED) in high-risk hypertensive patients and its relation to beta-blockade agents. ED was assessed for 6 months by the International Index of Erectile Dysfunction (IIEF).[2] The IIEF is a 15-item, 5-domain, 30-point ED questionnaire that has been proven to be valid and reliable in previous trials. The minimal clinically important difference is 4, but varies based on ED severity.

Compared with other beta-blockers, nebivolol was associated with higher scores in every parameter of the IIEF questionnaire by 1 to 9.5 points, but statistical analysis was not reported. Patients treated with nebivolol had a lower prevalence of ED (odds ratio 0.27; 95% CI, 0.09–0.78) compared with hypertensive patients not receiving nebivolol. Prevalence of ED in patients receiving atenolol and carvedilol was not significantly different than in patients not receiving these medications.[2]

A 2006 prospective study evaluated the risk of ED in 44 men (ages 31–65 years) with hypertension taking beta-blockers (atenolol 50–100 mg/d, metoprolol 100 mg/d, or bisoprolol 10 mg/d).[3] Patients were initially maintained on their previously prescribed beta-blocker for at least 6 months (range 6 months to 20 years) and an ED evaluation was performed using the IIEF. All patients were then switched to an equipotent dose of nebivolol (5–10 mg/d) for 3 months. Patients were then asked to repeat the same questionnaire. The mean dose of atenolol was 63 mg/d while the mean nebivolol dose was 6.45 mg/d.

Twenty-nine of the 44 (65.9%) patients initially exhibited ED. The erectile function of 20 of these 29 (69.0%) patients improved significantly after a 3-month period of nebivolol administration (*P*<.01). Erectile function normalized in 11 of these 29 patients (*P*<.01). Patients' mean erectile function score improved significantly after nebivolol administration (mean IIEF score 17 vs 22; *P*<.01).[3]

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Does application of antibiotic ointment to wounds after minor elective skin lesion procedures improve healing or decrease the rate of infection?

EVIDENCE-BASED ANSWER

Used for wound care after minor elective skin procedures, double or triple antibiotic ointments do not appear more effective than nonantibiotic ointment (SOR: **B**, based on small consistent RCTs).

A 2011 double-blind RCT (N=30, mean age 61 years) evaluated the safety and efficacy of petrolatum-based ointment compared with antibiotic-based ointment applied to wounds after removal of seborrheic keratosis.[1] Each subject had 2 seborrheic keratoses removed by scalpel, but depth of incision was not reported. No sutures were used and each wound was treated with either petrolatum-based ointment (Aquaphor Healing Ointment®, AHO) or double antibiotic-based ointment (Polysporin/bacitracin). Wound healing,

subjective irritation, and overall wound appearance was assessed at 7, 14, and 28 days using 5-point visual scores. Appearance was judged from photographs by clinicians blinded to treatment.

No difference was noted in erythema, edema, epithelial confluence, crusting, scabbing, overall wound healing, or appearance at any time point between the 2 groups. Irritation was increased at 1 week in the antibiotic ointment group compared with the AHO group (mean score 0.40 vs 0.20; $P<.05$). There was 1 case of allergic contact dermatitis in the antibiotic group.[1]

A 2011 double-blind RCT (N=20) evaluated the wound healing properties of 3 topical wound care ointments.[2] Men and women aged 25 to 50 years were included, and individuals with known sensitivity or allergy to skin care products were excluded. Four uniform laser wounds were created in each subject, penetrating to the dermis, and 3 wounds were treated 3 times daily for 18 days with either petroleum-based ointment (AHO), triple antibiotic ointment (Polysporin/bacitracin/neomycin), or double antibiotic ointment. One wound was left untreated. All wounds were assessed on a 0 to 4 visual analog scale for erythema, edema, and scabbing (lower scores better) as well as epithelial confluence and general appearance (higher scores better) by blinded evaluators at 4, 7, 11, 14, and 18 days.

AHO scored significantly better than double and triple antibiotic ointment in wound erythema (day 7, 11, 14, 18), edema (day 4, 7), epithelial confluence (day 7, 11, 14, 18), and general wound appearance (day 7, 11, 14, 18) ($P<.05$ for all comparisons). No significant differences were noted in any outcome measures at any time point between the triple and double antibiotic groups and no consistent differences were found between untreated and treated wounds. No infections or adverse events were reported in any of the study groups.[2]

A 2011 RCT (N=20) evaluated wound healing in skin of patients who identified as African American.[3] Patients aged 18 to 70 years were eligible for enrollment. Individuals with any known allergy or sensitivity to the test materials were excluded. The study enrolled 20 African American patients who had removal of dermatosis papulosa nigra using fine curved blade scissors from both sides of the face. One wound was treated with a petroleum-based ointment (AHO) and the other was treated with double antibiotic ointment for 21 days. All wounds were assessed for erythema, edema, epithelial confluence, crusting, scabbing, and melanin confluence or postinflammatory hyperpigmentation using 5-point visual scores by blinded evaluators at 1, 3, 7, 10, 14, and 21 days.

No difference was noted in any clinical outcome measure at any time point between the AHO and double antibiotic groups. Subjective irritation (burning, itching, stinging, tightness, and pain) was similar between the 2 treatments. No infections or adverse events were reported.[3]

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

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What is the differential diagnosis of otalgia in an adult with a normal ear examination?

EVIDENCE-BASED ANSWER

The most common causes of secondary otalgia (ear pain caused by a nonotologic source) in adults are likely dental disease, temporomandibular joint (TMJ) disorder, and cervical spine arthritis (SOR: **C**, based on case series and chart review).

A retrospective case series of adult patients (N=7,004, aged 19–83 years) referred to a otolaryngology practice found the incidence of otalgia with normal ear examination was 8.8%.[1] Reported etiologies were dental otalgia (38.4%), TMJ disorder (35.4%), cervical arthritis (8.4%), neuralgia (4.9%), aerodigestive (3.7%; commonly tonsillitis, pharyngitis, sinusitis, or gastroesophageal reflux), malignant infratemporal fossa (IFT) tumors (2.9%), and other (6.4%).

A poorly described retrospective chart review of 133 patients referred to a tertiary academic medical center from 2002 to 2006 found that cervical spine degenerative disease was the identified cause of secondary otalgia in 37%

of adult patients (aged 36–78 years) with unspecified ear pain, normal otologic examination, and no history of ear surgery.[2] Other less common causes of secondary otalgia from this review included referred pain from specific cranial nerves (CN) such as trigeminal neuralgia, mandibular osteomyelitis, or parotiditis from CN V, acoustic neuroma or herpes zoster from CN VIII, pharyngeal tumor or glossopharyngeal neuromas from CN IX, and laryngeal pharyngeal reflux or cricopharyngeal spasm from CN X.

A recent narrative review article noted the differential diagnosis for otalgia due to dental conditions includes acute pulpitis (commonly molar caries), acute or chronic periodontitis, acute apical abscess, acute or chronic periodontal abscess, and pericoronitis (inflammation of impacted third molars).[3]

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Does vitamin D level affect outcomes in patients with systemic lupus erythematosus (SLE)?

EVIDENCE-BASED ANSWER

Vitamin D supplementation in patients with SLE who have vitamin D insufficiency decreases disease activity (SOR: **B**, single RCT and case series). Vitamin D serum concentration is inversely related to SLE disease activity (SOR: **B**, cross-sectional study).

A double-blind RCT in 228 premenopausal women and 39 men with SLE examined if vitamin D supplementation altered the SLE disease activity index (SLEDAI), which assesses disease severity.[1] Patients (average age 38.8 years) with a mean SLE disease duration of 8.2 years were randomized to 2000 IU/d vitamin D or placebo. The mean vitamin D level at baseline for patients in treatment and placebo groups, respectively, was 19.8 and 28.7 ng/dL (10–30 ng/dL indicates insufficient level). SLEDAI scores range from 0 to 105 and scores of 5 or more are generally considered to be clinically significant and an indication for treatment.

After 12 months of vitamin D supplementation, the prevalence of vitamin D insufficiency decreased from 69% to 19%, while the SLEDAI significantly improved from a mean score of 4.9 to 3.2 (P=.01). The prevalences of vitamin D insufficiency at baseline and after 12 months in the placebo group were 68% and 61%, respectively, and the SLEDAI score in the placebo group did not change significantly (4.8 to 4.5; P=.69). Vitamin D levels correlated inversely with SLEDAI scores (correlation coefficient [r] –0.583; P<.05).[1]

A case series involving female patients with SLE (N=1,006; mean age 49.6 years) evaluated whether an increase in vitamin D level had any effect on SLE disease activity over 128 weeks.[2] Disease activity was measured using the SELENA-SLEDAI, which is similar to SLEDAI with the same range of 0 to 105. Because recent studies recommended a serum vitamin D level of at least 30 to 40 ng/mL in adults, patients with vitamin D levels less than 40 ng/mL received vitamin D supplementation.

Seventy-six percent (n=763) of all patients in the study were found to have serum vitamin D levels less than 40 ng/mL, and were given 50,000 units of vitamin D2 weekly and 200 units of vitamin D3 with calcium twice daily.[2]

In patients with vitamin D less than 40 ng/mL, a 20-unit increase in vitamin D level decreased the mean SELENA-SLEDAI score by 0.22 (95% CI, –0.41 to –0.02). This change corresponded with a decrease in the odds of having a SLEDAI score of 5 or more by 21% (95% CI, 1–37). There was no change in SLE disease activity by increasing vitamin D level in patients who had already had levels more than 40 ng/mL.[2]

A cross-sectional retrospective study in 378 patients from Europe assessed the correlation between SLE disease activity and vitamin D serum concentration.[3] SLE disease activity was measured using the SLEDAI–2000 in 278 patients and the European Consensus Lupus Activity Measurement (ECLAM) scores in 100 patients (exact composite for scoring systems was not available). Serum vitamin D level was measured on the same day the disease activity was scored by the investigators. Data from the 2 scoring systems were converted into 1 standardized value to obtain univariate summary.

This study showed a weak, but statistically significant negative correlation between SLE disease activity and serum

vitamin D concentration (r –0.12; P=.018). Mean serum vitamin D concentrations were found to be lower in patients with active SLE disease (ie, SLEDAI score >3 or ECLAM score >1) compared with patients who had quiescent disease (mean 17.8 vs 24.3 ng/mL; P<.0001).[3]

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Is garcinia cambogia more effective for weight loss than diet and exercise?

EVIDENCE-BASED ANSWER

No. Garcinia cambogia plus diet and exercise does not cause a meaningful increase in weight loss over diet and exercise alone (SOR: **B**, meta-analysis of poor-quality RCTs and 2 RCTs).

The active ingredient in garcinia cambogia (*Garcinia gummi-gutta*) is hydroxycitric acid (HCA), which may prevent fat formation and suppress appetite through different mechanisms.

A systematic review examined 12 RCTs (N=706 patients) of overweight/obese patients comparing oral HCA (1–2.8 g/d) to placebo over 2 to 12 weeks.[1] All patients continued with general dietary and exercise interventions.

Nine studies (n=459), similar enough to be included in a pooled data analysis, found more weight loss with HCA than placebo (mean difference [MD] –0.88 kg; 95% CI –1.8 to 0), although by a clinically insignificant amount. In most studies, no statistically significant difference was found between the HCA and control groups for side effects of headache, skin rash, common cold, and gastrointestinal (GI) symptoms. Limitations of the studies included small sample size; poor descriptions of randomization, blinding, and allocation concealment; and differences in HCA dosage.[1]

The largest RCT from the above review, and the only one with an intention-to-treat analysis, examined the effect of garcinia cambogia extract (1,500 mg/d) on body weight and fat mass versus placebo over 12 weeks in 135 patients (ages 18–65, BMI 27–38 kg/m^2).[2] All patients were prescribed a high-fiber, low-energy diet.

Garcinia cambogia did not produce a statistically significant weight loss compared with placebo (mean weight loss 3.2 vs 4.1 kg; P=.14). No significant differences were noted in percent body fat mass loss when accounting for age, sex, and pretest percentage of fat mass (mean percent body fat loss: garcinia cambogia 1.4%, placebo 2.2%; P=.21). Adverse events in the garcinia cambogia group (headache, upper respiratory tract symptoms, and GI symptoms) were not more common than in the placebo group. Study limitations included a small sample size and timing/dosage of HCA.[2]

An RCT of 86 patients (ages 20–50, BMI 23–29 kg/m^2) examined the effectiveness of Glycine max (soybean) leaves (2 g/d), garcinia cambogia extract (2 g/d), or starch placebo on weight loss versus placebo over 10 weeks.[3] Patients maintained their regular diet throughout the study.

Garcinia cambogia did not significantly increase weight loss (0.65 kg) versus placebo (0.68 kg; P>.05). No adverse effects were reported. Study limitations included sex differences despite randomization and small sample size.[3]

An RCT of 98 patients (ages 21–55, BMI 25.2–39.6 kg/m^2) examined the effect of garcinia cambogia (1 g HCA twice daily) versus placebo on weight loss over 12 weeks.[4] All patients were instructed to follow a 1,500 calorie diet and a daily exercise regimen.

Garcinia cambogia did not significantly increase weight loss versus placebo (mean weight loss [SD] –2.0 kg [2.6] vs 1.5 kg [3.5]; P=.27). However, when corrected for amount of exercise, garcinia cambogia resulted in 24.1 g more weight loss per hour of exercise over placebo (P=.046).[4]

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Do the same infants who develop seborrheic dermatitis also develop atopic dermatitis?

EVIDENCE-BASED ANSWER

Infants with infantile seborrheic dermatitis (ISD) are more likely to develop infantile atopic dermatitis (IAD) than infants without ISD (SOR: **C**, case series compared with historical controls). Similarly, infants with IAD are more likely to have had a history of ISD earlier in life than infants without IAD (SOR: **B**, case control study).

In a 2014 retrospective case series in Greece, 87 infants with ISD were identified to determine how many developed IAD.[1] The diagnosis of ISD was made through the Beare and Rook diagnostic criteria. Included infants needed to display nonpruritic, erythematous skin lesions with overlying scales or crusts in various locations, including the eyebrows, scalp, inguinal, or flexural regions. The diagnosis of IAD was made through the UK Working Party diagnostic criteria. To fulfill these criteria, patients needed to display visible pruritic eczema in primarily the flexor regions (extensor regions if under 18 months), symptoms before the age of 2 years, and a personal history of dermatitis, dry skin, asthma, or allergic rhinitis. Over 4.8 years, data were available on 49 of the 87 children.

Thirty of the initially identified 87 infants (34.4%) with ISD developed IAD. The 34% of infants with ISD developing IAD were significantly greater than the 10.7% prevalence of IAD from another study in the same region matched for age (P<.001).[1]

In 2002, a case-control study in Peru examined 96 infants 2 to12 months old with a diagnosis of IAD and 96 age-, region-, and sex-matched controls to determine how many had a history of ISD.[2] The diagnosis of ISD was also made via the Beare and Rook diagnostic criteria, whereas the diagnosis of IAD was made with the Hanifin and Rajka criteria. To meet the latter criteria, the children needed to have pruritic dermatitis on primarily the flexor surfaces (extensor surfaces in infants), chronic dermatitis, as well as a personal or family history of a respiratory allergy. In addition minor criteria including facial features or irritants and triggers were also necessary to meet the diagnostic criteria.

A positive history of ISD was found in 49% of the IAD patients, whereas only 17% of the control group had a positive history of ISD (P<.001).[2]

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In adults with esophageal spasms, are noninvasive pharmacologic treatments superior to nonpharmacologic treatments?

EVIDENCE-BASED ANSWER

No controlled trials have been conducted involving nonpharmacologic treatments for esophageal spasm. Nifedipine reduces esophageal pressures but does not improve symptoms (SOR: **C**, 1 randomized crossover trial and 1 nonrandomized crossover trial). Diltiazem reduces esophageal pressures and has inconsistent effects on chest pain (SOR: **C**, 2 randomized crossover trials).

A 1987 randomized double-blind crossover trial (N=20) examined the effect of nifedipine on chest pain in adults with esophageal spasms.[1] Mean patient age was 50 years (range 31–69 years), 60% were male, and all had daily symptoms. The diagnosis of esophageal chest pain was "definite" in 11 patients (positive chemical provocative test with edrophonium or balloon distention of midesophagus) and 9 patients had "at least suspected" esophageal chest pain (abnormal baseline manometry). Nifedipine was increased from 10 to 30 mg PO TID over 6 weeks with matching placebo in the control group. Crossover for an additional 6 weeks was preceded by a 2-week washout. Manometry and a symptom scale (improved, stable, worse) were measured at the end of each 6-week period.

Nifedipine reduced distal esophageal and lower esophageal sphincter pressures compared with placebo (123 vs 198 mmHg; P<.005). Symptoms were unchanged with

improvement reported by 6 patients while taking nifedipine and by 6 while taking placebo (8 reported no change in symptoms). No patients dropped out and the mean maximum daily dose of nifedipine was limited to 51 mg by adverse events (facial flushing, peripheral edema, headaches, lightheadedness, and nervousness).[1]

A 1987 nonrandomized crossover trial (N=8) evaluated the effect of nifedipine on chest pain in adults with esophageal spasm.[2] Mean patient age was 39 years (range 31–57 years), 50% were male, and all had diffuse spasm by manometry with severe symptoms. Nifedipine was titrated from 10 to 30 mg PO TID (mean daily dose 64 mg/d) and maintained at the maximum tolerated dose for 4 to 8 weeks. Patients were switched to placebo capsules sometime between 4 and 8 weeks and for the final 4 weeks all patients were on placebo. Pain severity (3-point scale: mild, moderate, severe), nighttime awakenings and dysphagia were recorded daily in symptom diaries during the maintenance period and data from the 14 days following crossover were excluded from analysis. Outcomes were based on symptom scores while on nifedipine and after the "washout" period.

There were no significant differences in the frequency or severity of pain and mean daily pain scores were also similar with nifedipine versus placebo (1.6 vs 1.5; $P>.05$).[2]

A 1991 double-blind crossover trial (N=14) evaluated the effect of diltiazem on chest pain in patients with high amplitude esophageal contractions referred to gastroenterology for evaluation of noncardiac chest pain or dysphagia.[3] Mean patient age was 50 years (range 24–60), 57% were male, and mean distal esophagus pressure was 191 mmHg. Patients were randomized to 8 weeks of diltiazem titrated from 60 to 90 mg PO QID or matching placebo before crossover for another 8 weeks without washout. The chest pain index score assessed at weeks 2, 4, and 8 ranges from 0 to 20 (greatest daily severity of chest pain plus dysphagia; each on a 0–10 scale).

Diltiazem therapy decreased distal esophagus contraction amplitude (measured at 8 cm above lower esophageal sphincter) versus placebo (136 vs 168 mmHg; $P<.02$) with no change in contraction duration. Although the mean chest pain index was reportedly reduced in the diltiazem group versus placebo, neither mean differences nor actual scores were reported.[3]

A 1990 double-blind crossover trial (N=8) evaluated the effect of diltiazem for chest pain in patients with diffuse esophageal spasm.[4] Mean patient age was 40 years (range 32–59), 75% were male, and spasm was confirmed by manometry. There were 2 randomly assigned 4-week treatment periods with diltiazem 60 mg TID or placebo separated by a 2-week washout. Participants recorded symptom frequency and severity (using a visual analogue scale) for chest pain and dysphagia in diaries. Chest pain and dysphagia indices were derived by multiplying daily frequency with intensity. No significant differences in chest pain or dysphagia were reported between groups.

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In patients with type 2 diabetes, is intensive glucose control more cardioprotective than standard glucose control?

EVIDENCE-BASED ANSWER

No. Intensive glycemic control is not superior to conventional glycemic control for cardioprotection in patients with type 2 diabetes when measuring all-cause mortality, cardiovascular (CV) mortality, nonfatal myocardial infarction (MI), congestive heart failure (CHF), arrhythmias, and reinfarction rates. In some North American populations, intensive glycemic control leads to increased CV and all-cause mortality (SOR: **A**, meta-analyses of RCTs)

A 2015 meta-analysis of 17 RCTs (N= 34,967) compared the efficacy of intensive blood glucose control versus standard treatment in trials from North America (7 RCTs, n=13,287) and the rest of the world (10 RCTs, n=21,680).[1] The definition of intensive therapy was not consistent across trials, with different

hemoglobin A1C (HbA1C) goals used. Outcomes included all-cause mortality, CV mortality, major macrovascular events, major microvascular events, and severe hypoglycemic events. The North American trials had an average age of 57, average duration of diabetes of 5.2 years, and baseline A1C of 10.6%.

The mean decrease in HbA1C in the intensive group was 2.2% and the mean decrease in the standard treatment group was 0.83%. Analysis revealed no significant difference between intensive and standard glucose control in all-cause mortality (17 RCTs, n=34,967; odds ratio [OR] 1.03; 95% CI, 0.9–1.13) or CV mortality (OR 1.09; 95% CI, 0.9–1.32). In the North American subset, all-cause mortality (OR 1.21; 95% CI, 1.05–1.4) and CV mortality (OR 1.4; 95% CI, 1.05–1.9) were significantly increased in the intensive therapy group. No significant difference in nonfatal MI and nonfatal stroke were found between the intensive and standard groups. Additionally, in North America, risk of severe hypoglycemia (not defined) was significantly increased with intensive glycemic control (OR 3.52; 95% CI, 3.07–4.03). Included trials were heterogeneous related to time periods, patient populations, and interventions to achieve glucose control.[1]

A 2013 meta-analysis of 3 RCTs (N=2,113) not included in the above meta-analysis compared intensive with standard glycemic control (not defined) among patients with type 2 diabetes who had a recent acute MI.[2] The primary outcome studied was all-cause mortality, and follow-up was between 3 months and 3 years.

No significant reduction in mortality was demonstrated with intensive glycemic control compared with standard control (relative risk [RR] 0.94; 95% CI, 0.66–1.34). Secondary outcomes included rates of CHF exacerbation, arrhythmias, and reinfarction, which were found to be no better in the intensive control group than the standard control group. Intensive control was associated with a significant increased risk for hypoglycemic episodes (RR 13.4; 95% CI, 3.7–49).[2]

The 2016 American Diabetes Associates (ADA) guidelines for glycemic control stated that providers must be careful to prevent severe hypoglycemia in patients with advanced diabetes.[3] Aggressive control of glucose levels was not recommended for this population, citing the potential risks of intensive glycemic control. The ADA recommended that glycemic control be tailored to individual patients and A1C goals based on several factors, including duration of diabetes, life expectancy, comorbid conditions, known CVD or microvascular conditions, hypoglycemia unawareness, and individual patient preferences (Grade B recommendation: supportive evidence from well-conducted cohort or case-control studies).

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Is transabdominal ultrasound measurement of single deepest vertical pocket effective for ruling out oligohydramnios and predicting complications?

EVIDENCE-BASED ANSWER

Single deepest vertical pocket (SDVP) leads to fewer diagnoses of oligohydramnios than amniotic fluid index (AFI). Use of the SDVP test decreases rates of both labor induction and cesarean sections for fetal distress compared with AFI without differences in other neonatal outcomes (SOR: **A**, meta-analysis of RCTs and single RCT). Yet SDVP has poor sensitivity for oligohydramnios compared with the "gold standard" of dye-dilution spectrophotometry (DDS) for amniotic fluid volume assessment (SOR: **C**, disease-oriented evidence).

A 2009 meta-analysis of 5 RCTs (with 3,226 women) compared the use of AFI and SDVP in both high- and low-risk singleton pregnancies for the prevention of unfavorable pregnancy outcomes.[1] Two trials evaluated high-risk patients (definition not reported) using serial biophysical profiles, 2 trials evaluated low-risk patients as part of a post-term evaluation, and 1 trial evaluated all women admitted in labor.

TABLE

AFI versus SDVP for various pregnancy outcomes[1]

Outcome	RR (95% CI)	Comment
NICU admission	1.04 (0.85–1.26)	No difference in outcomes between AFI and SDVP
Umbilical artery pH <7.1	1.10 (0.74–1.65)	
Presence of meconium	1.09 (0.90–1.30)	
Apgar score <7 at 5 minutes	1.15 (0.70–1.89)	
Cesarean section (in absence of fetal distress)	1.09 (0.92–1.29)	
Diagnosis of oligohydramnios	2.39 (1.73–3.28)	Increased risk with AFI
Inductions of labor	1.92 (1.50–2.46)	
Cesarean section for fetal distress	1.46 (1.08–1.96)	

AFI=amniotic fluid index; CI=confidence interval; NICU=neonatal intensive care unit; RR=risk ratio; SDVP=single deepest volume pocket.

Using transabdominal ultrasound, oligohydramnios was ruled out if a single pocket of amniotic fluid measured 2 cm deep by 1 cm wide or more or if 4 quadrant AFI measurements totaled more than 5 cm.

No difference was noted between SDVP and AFI in outcomes such as neonatal intensive care unit (NICU) admission, umbilical artery pH less than 7.1, Apgar score less than 7 at 5 minutes, presence of meconium, cesarean section (in the absence of fetal distress), or assisted vaginal delivery (see **TABLE**). However, the utilization of AFI significantly increased the diagnosis of oligohydramnios, and the rates of both labor induction and cesarean section for fetal distress (see **TABLE**).[1]

A more recent multicenter RCT conducted at 4 hospitals in Germany from July 2012 through September 2013 compared SDVP and AFI in 1,052 women with term singleton pregnancies presenting for delivery or a "pre-labor" examination with a primary outcome of NICU admissions.[2] Exclusion criteria included premature rupture of membranes, previous cesarean section, intrauterine fetal death, fetal malformations, no ultrasound in the previous week, or a contraindication to vaginal delivery. Those receiving the diagnosis of oligohydramnios (AFI ≤ 5 cm or SDVP <2 cm x 1 cm) underwent induction of labor.

Inductions were more frequent in the AFI group than in the SDVP group (12.7% vs 3.6%; risk ratio [RR] 3.5; 95% CI, 1.8–7.0), as was diagnosis of oligohydramnios (9.8% vs 2.2%; RR 4.5; 95% CI, 2.2–8.6). No difference was found in rate of NICU admission (4.2% vs 5.0%; RR 0.85; 95% CI, 0.48–1.5).[2]

In a 2004 study, ultrasound measurements and DDS volumes were prospectively collected from 291 women with singleton pregnancies to assess the accuracy of SDVP in detecting oligohydramnios.[3] The study population included consenting women undergoing amniocentesis for evaluation of fetal lung maturity or subclinical chorioamnionitis at a single US medical center between March 1994 and 2001. In the DDS method, a fixed amount of a nontoxic, physiologically inert dye was injected into the amniotic cavity during amniocentesis. The dye was allowed to fully diffuse, then a sample was removed and assayed for extent of dilution.

DDS identified 75 pregnancies (26%) with oligohydramnios (total amniotic fluid volume <5th percentile) and, of these, SDVP identified only 2, yielding a sensitivity of 3% and diagnostic accuracy of 64%. Of note, wide-scale use of DDS is clinically impractical because the invasive procedure is limited to patients undergoing amniocentesis.[3]

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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 Navy Medical Department, the Navy at large, or the Department of Defense.

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Are probiotics effective for the prevention of upper respiratory infections in children?

EVIDENCE-BASED ANSWER

It depends. Daily supplementation with at least 10^9 colony forming units (cfu) of either *Lactobacillus rhamnosus* GG or *L acidophilus* reduces the frequency of upper respiratory infections and the symptoms of fever and cough. When combined with *Bifidobacterium lactis*, such supplementation also reduces the occurrence of rhinorrhea (SOR: **B**, RCTs in Croatia and China). Supplementation with *Bifidobacterium* alone does not appear to decrease the frequency of upper respiratory infections (SOR: **B**, single RCT in Finland).

A 2010 double-blinded RCT (N=281, ages 13–86 months) compared daily probiotic supplementation with *L rhamnosus* GG 10^9 cfu with placebo for the prevention of respiratory infections over 3 months.[1] Participants were children who attended day care centers at 4 locations in Croatia. Children with cow's milk allergy, receiving probiotic prior to enrollment, with severe chronic illness/immunodeficiency, or who disliked fermented milk products were excluded. Study investigators contacted the parents of the study participants every 10 days to determine if the children developed respiratory symptoms. If parents reported concerns, local general practitioners would then see the child and diagnose an infection.

Probiotic supplementation significantly reduced the frequency of respiratory infection (relative risk [RR] 0.63; 95% CI, 0.51–0.79, number needed to treat [NNT]=5). Additionally, supplementation reduced the number of children with upper respiratory infection (RR 0.66; 95% CI, 0.52–0.82, NNT=5) and respiratory infection lasting longer than 3 days (RR 0.57; 95% CI, 0.41–0.78, NNT=5). No side effects or adverse events were noted during this study.[1]

A 2009 RCT (N=326, ages 3–5 years) at a group child care center in China over 6 months compared single-strain probiotic, double-strain probiotic, and placebo for reduction of fever, cough, and rhinorrhea.[2] Participants were healthy children not taking probiotics and with no known preexisting diseases, anatomic alterations, or contraindications to dairy products. Children received *L acidophilus* 10^{10} cfu, *L acidophilus* combined with *B lactis* 10^{10} cfu (total), or placebo.

The odds of developing symptoms of fever or cough were significantly reduced in both intervention arms as well as the odds of developing rhinorrhea in the double-strain arm compared with placebo (see **TABLE**).[2]

A 2012 RCT (N=501, ages 2–6 years) compared *L rhamnosus* GG 10^8 cfu with placebo to assess rate of respiratory illness.[3] Sixty daycare centers in Finland recruited children attending 5 days a week. Children with milk allergy, lactose intolerance, chronic disease, continuous microbial medication, regular use of oral corticosteroids, diabetes, or simultaneous participation in other clinical trials were excluded.

No significant difference was noted over 28 weeks in the number of days with a respiratory symptom (incidence

TABLE

Odds of developing fever, cough, and rhinorrhea in children 3 to 5 years old by probiotic supplementation[2]

Intervention	Odds ratio for indicated outcome (95% CI)		
	Fever	Cough	Rhinorrhea
Lactobacillus acidophilus 10^{10} cfu vs placebo	0.57[a] (0.44–0.90)	0.59[a] (0.39–0.96)	0.93 (0.57–1.5)
L acidophilus/ *Bifidobacterium lactis* 10^{10} cfu (total) vs placebo	0.34[a] (0.22–0.63)	0.44[a] (0.28–0.78)	0.52[a] (0.34–0.97)
L acidophilus/*B lactis* vs *L acidophilus*	0.74 (0.38–1.3)	0.84 (0.46–1.4)	0.65 (0.34–1.1)

[a]Statistically significant.

rate ratio [IRR] 0.97; 95% CI, 0.94–1.0) or the number of respiratory symptoms per month (IRR 1.1; 95% CI, 0.96–1.2). A limitation of this trial was the daily total cfu administered to the intervention group was only 10^8.[3]

A 2015 RCT (N=210, ages 1.5–7 years) compared the probiotic *B animalis* subsp. *lactis* 10^9 cfu with placebo for prevention of respiratory infections over 3 months at 3 daycare centers in Finland.[4] Children receiving probiotic products 2 weeks before or at the time of enrollment and those with severe chronic illness were excluded.

No difference was noted in the number of children with respiratory infections between the probiotic and placebo groups (IRR: 1.0; *P*=.88). No adverse events were reported.[4]

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Are electrotherapy modalities effective for reducing pain and improving function in patients with adhesive capsulitis (frozen shoulder)?

EVIDENCE-BASED ANSWER

Low-level laser therapy (LLLT), when compared with placebo or as an adjuvant to physical therapy, reduces pain and improves function for patients with adhesive capsulitis (AC). No other electromodalities have evidence of effectiveness (SOR: **B**, systematic review of low- and moderate quality RCTs). LLLT may improve pain and function associated with AC for up to 2 years in elderly patients (SOR: **C**, single case series).

A 2014 systematic review of 19 RCTs and trials with quasirandomized method of allocation (such as date of birth) evaluated electrotherapy modalities for treatment of frozen shoulder in 1,249 patients.[1] Patients were 16 years old or older with AC as defined by the study for any duration, but without a history of trauma or systemic inflammatory disease such as rheumatoid arthritis, osteoarthritis, hemiplegic shoulder, or shoulder pain due to complex myofascial pain condition. Studies evaluated multiple electrotherapy modalities, including therapeutic ultrasound, LLLT, transcutaneous electric nerve stimulation, pulsed electromagnetic field therapy, interferential current, phonophoresis, iontophoresis, and continuous short wave diathermy. The main outcomes were pain reduction of at least 30%, overall pain improvement, and function improvement based on a priori criteria with questionnaires.

The final conclusion of the Cochrane review was that only LLLT has evidence of benefit when compared with placebo or as an adjuvant to physical therapy for AC, and it was unclear whether the other modalities provided benefit alone or in combination with physical therapy. One trial (n=40) demonstrated LLLT for 6 days resulted in pain improvement compared with placebo (80% vs 10%; relative risk 8.0; 95% CI, 2.1–30.3). Another study (n=63) compared LLLT (n=31) with placebo (n=32), with both groups receiving physical therapy. Patients in the LLLT group in that study had lower pain scores on a 100-point scale at 4 weeks (mean difference [MD] 19 points; 95% CI, 15–23) and at 4 months (MD 13 points; 95% CI, 9–16).[1]

A 2015 2-year case series (N=35) of older adult patients (mean age 65 years) evaluated the management of AC with LLLT.[2] Patients were included if they presented within 6 weeks of onset of symptoms, failed to respond to NSAIDs and 4 weeks of conventional physical therapy, and had AC confirmed via contrast-enhanced magnetic resonance imaging without other pathology such as rotator-cuff tear. Exclusion criteria included prior shoulder surgery, prior cerebrovascular accident affecting upper extremities, and potential contraindications for LLLT, such as previous tumor or ongoing sepsis. Patients were evaluated using the Constant–Murley (CM) score, which assesses pain and function. The score is measured on a 100-point scale, with a higher score implying less pain and better function.

Apart from the 4 shoulders of 2 patients who did not show clinical response to LLLT and required surgery, the remaining 46 shoulders had improved CM scores initially after treatment and at 2 years. Prior to LLLT, patients had an average CM

score of 59 (range 57–62); after initial treatment, patients had a mean score of 71, which was maintained for 2 years (range 68–73; $P<.05$).[2]

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Should women with a single first-degree relative with breast cancer begin mammography at age 40?

EVIDENCE-BASED ANSWER

Do consider it. A woman with a single first-degree relative (mother or sister) affected by breast cancer has about a 1.5 times higher risk of developing breast cancer and is likely to experience a similar risk-to-benefit ratio from beginning mammography at age 40 as an average-risk woman beginning mammography at age 50 (SOR: **B**, cohort study and modeling study). The US Preventive Services Task Force (USPSTF) recommends consideration be given to starting mammography at age 40 based on individual factors including family history in a first-degree relative (SOR: **B**, evidence-based guideline), while the American Cancer Society (ACS) suggests all women be given the option of initiating screening at age 40. (SOR: **C**, consensus guideline).

A 2012 prospective cohort study collected questionnaires every 2 years for 26 years from 69,805 women to assess the role of family history, including age of diagnosis, in the risk of developing breast cancer.[1] Participants who indicated a family history of breast cancer involving a mother or sister (first-degree relatives) were asked at what age their relative was diagnosed (<50 years or >50 years of age). Incident cases of breast cancer were confirmed via review of medical records.

Compared with women who had no family history, women whose mother was diagnosed before age 50 were at a significantly increased risk for developing breast cancer (relative risk [RR] 1.7; 95% CI, 1.4–2.1), and to a lesser degree, those whose mother was diagnosed at 50 or older (RR 1.4; 95% CI, 1.2–1.5). Similarly, women with a sister diagnosed with breast cancer before the age of 50 were at increased risk for developing breast cancer compared with women without a family history (RR 1.7; 95% CI, 1.4–2.0), as were women with a sister diagnosed after the age of 50 (RR 1.5; 95% CI, 1.3–1.8).[1]

A 2015 modeling study using the breast cancer–related characteristics of the 1970 birth cohort of US women evaluated the risk-to-benefit ratio of mammography initiation beginning at ages 40, 45, or 50 years.[2] The study used 6 different models to simulate outcomes for synthetic patient cohorts by incorporating known data on cancer biology, screening behavior, and treatment effectiveness. Analyses were conducted to determine how the risk-to-benefit ratio shifted if the screening approach considered breast cancer risk factors including family history of 1 first-degree relative with breast cancer.

The study found that the risk increase associated with having a first-degree relative with breast cancer resulted in similar benefits and harms from biennial mammography between ages 40 and 74 as biennial mammography in average-risk women from 50 to 74 years of age. Benefits included a projected 11 breast cancer deaths averted per 1,000 women screened versus 4.5 (no test of significance given). Harms included 1,678 false-positive results per 1,000 women screened versus 1,019 (no test of significance given) and 34 overdiagnosed cases per 1,000 women screened versus 17 (no test of significance given).[2]

At the time of this writing, the USPSTF recommended initiating mammography in average-risk women at 50.[3] In women 40 to 49 years of age, the USPSTF suggested the decision to start mammography be individualized to the patient (Grade C recommendation against routinely providing the service as the net benefit is small), and that women with a parent, sibling, or child with breast cancer would likely benefit more than average-risk women who begin screening in their 40s.

The 2015 ACS recommendation stated that average-risk women should start mammography at age 45, but that women should be given the option to start mammography at age 40 ("Qualified Recommendation," most women would

want the suggested course of action, but many would not); updated ACS guidelines for higher risk women are pending.[4]

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What are the best pharmacologic smoking cessation options for patients with mental health conditions?

EVIDENCE-BASED ANSWER

Bupropion, with or without nicotine replacement therapy (NRT), as well as fluoxetine and paroxetine have no long-term effect on smoking cessation in patients with depression. Similarly, bupropion, with or without transdermal nicotine patches, and varenicline have no long-term effect on smoking cessation in patients with schizophrenia, even though rates of cessation may be higher at the conclusion of active treatment (SOR: **A**, meta-analyses of RCTs).

A 2013 meta-analysis of 49 RCTs examined the effectiveness of various smoking cessation interventions in smokers with current or past depression.[1] Smokers were included in the review if they were experiencing, or had previously experienced, major depression according to DSM-IV criteria or depressive symptoms per multi-item scales.

In the studies of patients with current depression, bupropion 150 mg BID for 7 to 24 weeks showed no effect on abstinence at 6 months (4 trials, n=355; risk ratio [RR] 1.3; 95% CI, 0.78–2.2) compared with placebo. Bupropion 150 mg BID plus NRT for 9 weeks compared with placebo plus NRT also had no effect (1 trial, n=55; RR 1.9; 95% CI, 0.38–9.7). Fluoxetine 20 to 40 mg/d for 12 to 14 weeks (2 trials, n=64) and paroxetine 20 to 40 mg/d for 9 weeks (1 trial, n=43) also demonstrated no effect on abstinence at 6 months (RR 1.0; 95% CI, 0.14–7.3; and RR 1.1; 95% CI, 0.34–3.5, respectively) compared with placebo.[1]

A 2013 meta-analysis of 34 RCTs evaluated the long-term efficacy of smoking cessation interventions in smokers with schizophrenia.[2] Smokers were included in the review if they had a current diagnosis of schizophrenia, according to the DSM or the International Classification of Diseases. Bupropion 150 to 300 mg/d for 4 to 12 weeks increased abstinence at the end of treatment compared with placebo (5 trials, n=230; RR 3.7; 95% CI, 1.7–8.1), but this effect vanished by 6 months (3 trials, n=104; RR 2.2; 95% CI, 0.50–9.6). Bupropion 150 mg BID combined with transdermal nicotine patches for 10 to 12 weeks compared with placebo plus transdermal nicotine patches had no significant effect on abstinence at 6 months (2 trials, n=110; RR 3.4; 95% CI, 0.87–13). Varenicline 1 mg BID for 12 weeks also had no effect on abstinence at the 6-month follow-up (1 trial, n=128; RR 5.1; 95% CI, 0.67–38), even though it did increase abstinence at the end of treatment (2 trials, n=137; RR 4.7; 95% CI 1.3–17).[2]

A 2014 meta-analysis of 7 RCTs (N=439) compared abstinence rates at the end of treatment with varenicline or placebo in smokers with schizophrenia.[3] Studies were included in the analysis if they were double-blinded, had a duration of at least 8 weeks, and included individuals with schizophrenia spectrum disorders. Both trials reporting the end of treatment outcome in the previous meta-analysis were included. The mean study duration for the trials was 16 weeks (range 8–52 weeks).

Compared with placebo, varenicline 1 to 2 mg/d did not improve smoking cessation (5 trials, n=322; RR 0.79; 95% CI, 0.58–1.1) at the end of active treatment.[3]

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Are patient satisfaction rates higher for birthing center births compared with hospital births?

EVIDENCE-BASED ANSWER

Women who deliver in a birthing center environment are twice as likely to rate their birthing experience as very positive compared with women delivering in a traditional hospital setting (SOR: **B**, based on a systematic review of RCT and inconsistent RCTs).

A 2012 Cochrane review of 9 RCTs with 11,503 women examined alternative versus conventional institutional settings for childbirth.[1] "Conventional institutionalized settings" were consistent with traditional labor wards where the bed is the focal point of the room with medical equipment in plain sight. "Alternative settings" focused on comfort, with some conveniences of a home setting and where the medical equipment is hidden from view unless needed. Control and comfort were emphasized.

More patients in the alternative care group compared with the conventional group gave "very positive views" of their intrapartum care (2 trials, n=1,207; 88% vs 44%; relative risk [RR] 2.0; 95% CI, 1.8–2.2).[1]

A 1997 RCT included in the 2012 Cochrane systematic review, but discussed separately here to compare differences in women with low-risk pregnancies, studied satisfaction with care in a midwife managed delivery unit (n=1,900) compared with an obstetrical consultant–led labor ward (n=944).[2] The women in the midwife-led unit had more continuity of care, choice, and control in labor management than the consultant-led group. Overall the satisfaction with the entire experience did not show a difference between the 2 groups.

An unblinded RCT in 2000 (included in the 2012 Cochrane systematic review, but not included in subset analysis as the survey response rate did not reach 80%) compared patients regarding outcomes and satisfaction of births conducted in a birthing center (n=100; 73 responded) versus standard hospital delivery (n=100; 75 responded).[3] The birthing center's goals were to provide a homelike environment with the provision of family-centered care. No difference was noted in the number of patients "happy and satisfied with care" between the birthing suite group and the hospital group (89% vs 86%; RR 0.99; 95% CI, 0.84–1.2).

A 2012 observational study (N=992) was conducted at a single health facility center comparing multilevel satisfaction among women treated at a modified in-hospital birth center versus standard institutional maternity care.[4] The modified birth center focused on a homelike environment with medical equipment hidden, an in-suite bathroom, and improved continuity of care from prenatal through postpartum care. Women in both groups were considered low risk.

The rates of satisfaction overall and in intrapartum and postpartum care were significantly higher in the modified birth center group compared with the standard care group (antenatal care odds ratio [OR] 2.1; 95% CI, 1.6–2.7; intrapartum OR 2.2; 95% CI, 1.7–2.9; and postpartum OR 1.7; 95% CI, 1.4–2.2).[4]

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What is the risk of transmission of an untreated wart?

EVIDENCE-BASED ANSWER

The risk of transmission of untreated warts to unaffected individuals is not clear, but having a family member with a wart doubles the risk of developing a wart, whereas having classmates with warts slightly increases the risk of developing a wart (SOR: **B**, single prospective cohort study). Although not directly related to exposure to untreated warts, public shower use, amount of public pool use, and failure to wear a protective sock when swimming are additional risk factors for developing warts (SOR: **B**, systematic review of case-control and cross-sectional studies). Experts have stated that warts can be locally spread by abrasion, and that skin-to-skin contact and fomite contact are part of interpersonal wart transmission (SOR: **C**, consensus guideline).

A prospective cohort study of 1,099 Dutch primary school children examined an association between degree of human papillomavirus (HPV) exposure and incidence of warts.[1] Hands and feet of all subjects were inspected at baseline and again at 11 to 18 months of follow-up. Parental questionnaires assessed HPV exposure as defined by preexisting individual warts, the presence of warts in family members, the prevalence of warts in a student's classroom, and environmental factors such as the use of public swimming pools, showers, or practicing sports barefoot.

In multivariate analysis, the study detected a dose-response increase in risk for the development of new warts with each additional HPV exposure (hazard ratio [HR] 3.5 per additional factor; 95% CI, 2.9–4.2). Among the individual risk factors found to contribute to wart development, the presence of at least 1 family member with a wart (HR 2.1; 95% CI, 1.5–2.9) and prevalence of warts in the school class (HR 1.2 per 10% increase in this prevalence; 95% CI, 1.0–1.4) were independent risk factors for the development of warts. Preexisting warts and use of public swimming pools did not meet significance as independent risk factors.[1]

A 2003 systematic review evaluated if wearing an occlusive dressing or sock while swimming reduced wart transmission.[2] Study inclusion criteria were not reported, but 5 studies were included: 1 case control and 4 cross-sectional studies (N not reported). The studies did not directly investigate effectiveness of prevention efforts to reduce transmission of warts.

One of these studies, of cross-sectional design and involving 146 adolescents, found that 27% of public shower users had warts compared with only 1.25% of adolescents who used the locker room but not showers. Another cross-sectional study of 773 bathers found the overall incidence of verrucas to be 4.8% "higher than previously recorded" among those who used a public swimming pool, although a baseline value in nonswimmers was not included. A third study, this time of case-control design and comparing 68 matched pairs of swimmers, found that those who wore socks were free from plantar warts while the non-sock group developed 9 new warts during study period.[2]

Expert opinion guidelines from the British Association of Dermatologists (BAD) and the American Academy of Dermatology (AAD) state that warts can be locally spread by abrasion and transmitted by skin-to-skin contact and fomite contact.[3,4] The AAD in a patient information document recommended early treatment of warts to promote clearance and prevent transmission. The AAD and BAD both recommended wearing pool shoes in public showers, locker rooms, and pool areas, keeping foot warts dry, and avoiding direct contact with, or abrasion of, a wart.

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Is naltrexone effective for smoking cessation?

EVIDENCE-BASED ANSWER

No. Naltrexone does not have a significant effect on long-term (6 month) smoking abstinence (SOR: **A**, systematic review of quality RCTs). Adding naltrexone to nicotine replacement therapy (NRT) results in better 12-week quit rates in heavy alcohol drinkers, but not moderate to light drinkers or nondrinkers (SOR: **B**, RCT). Naltrexone 25 mg along with NRT results in less weight gain during smoking cessation therapy compared with nicotine replacement alone, but higher doses do not (SOR: **B**, RCT).

A 2013 systematic review of 8 RCTs (N=1,213) evaluated the efficacy of the long-acting opioid antagonist naltrexone, 25 to 100 mg by mouth daily, in smoking cessation.[1] RCTs that compared opioid antagonists with placebo for smoking cessation and which reported data on abstinence for a minimum of 6 months as the primary outcome were included in the review. A secondary outcome was abstinence at the end of treatment. The average patient was 46 years old, 40% were female, and all were active smokers who desired to quit.

Naltrexone compared with placebo showed no significant difference in smoking cessation at 6 months (5 trials, n=450; relative risk [RR] 1.00; 95% CI, 0.66–1.5). Compared with

placebo, naltrexone augmented with NRT did not increase the proportion of people who quit smoking (4 trials, n=768; RR 0.95; 95% CI, 0.70–1.3).[1]

A 2014 double-blind RCT evaluated the efficacy of adding naltrexone 50 mg by mouth daily or placebo to NRT and behavioral support for smoking cessation in 315 smokers over 12 weeks.[2] Patients were divided into subgroups based on self-reported alcohol intake in the previous 6 months. Heavy drinking smokers (HDS) (n=69) were defined as individuals who averaged at least 2 heavy drinking episodes per month, compared with moderate-to-light drinkers (n=204), who had 1 or fewer drinking episodes per month, and nondrinkers (n=42).

Tobacco cessation rates at the end of 12 weeks were higher in the naltrexone HDS subgroup compared with the placebo HDS group (32% vs 14%; *P*=.02). No difference was noted in cessation rates between naltrexone and placebo in the moderate-to-light drinking smokers (25% vs 24%; *P*=.60). Nor was a difference found in the rate of tobacco cessation between naltrexone and placebo among nondrinking smokers, but the trend favored placebo (32% vs 10%; *P*=.24).[2]

A 2006 RCT of 400 smokers included in the 2013 systematic review assessed augmentation of NRT (21 mg patch for 6 weeks) with varying doses of oral naltrexone (0, 25, 50, or 100 mg daily) on smoking cessation and postcessation weight gain at 1 year.[3] The average patient was 46 years old, 47% were females, and all smoked at least 20 cigarettes daily.

No significant differences were noted in abstinence rates between the naltrexone augmentation groups and NRT alone, but the naltrexone 25-mg dose was associated with less mean weight gain than NRT alone (0.7 vs 1.9 kg; *P*=.01).[3]

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In hospitalized patients undergoing alcohol withdrawal, does fixed-dosing or as-needed (PRN) dosing of benzodiazepines result in better patient outcomes?

EVIDENCE-BASED ANSWER

Based on symptoms, as-needed dosing of benzodiazepines results in lower total dose of medication and shorter duration of treatment without a significant difference in complications compared with fixed dosing (SOR: **A**, consistent RCTs).

A 2014 double-blind RCT of 63 male patients, 18 to 60 years old and admitted for uncomplicated alcohol withdrawal, evaluated symptom-triggered versus fixed dosing of lorazepam for treatment of alcohol withdrawal.[1] The average duration of alcohol intake was 18.6 years. Patients were excluded from the study if they had other medical or psychological comorbidities. Symptom-triggered lorazepam treatment was 2 mg orally every 2 to 8 hours and fixed, tapering dosing of lorazepam started at 2 to 8 mg TID based on severity of alcohol withdrawal with additional dosing PRN. No scheduled placebo dosing was given to the symptom-triggered group.

Symptomatic assessment was based on the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) and patients and the medical provider administering the CIWA-Ar were blinded to treatment, but the nurses and treating psychiatrist were not. Both groups could receive additional dosing as needed at the discretion of the treating psychiatrist.[1]

The mean lorazepam dose administered was 9.5 mg for symptom-triggered versus 19.9 mg for fixed dosing (*P*<.001). Mean duration of treatment was 47.8 hours for symptom-triggered versus 146 hours for fixed dosing (*P*<.001). No significant difference was noted in complications between the groups for rates of seizures, delirium, hallucinations, increased severity of withdrawal symptoms, excessive sedation, and insomnia.[1]

In a 2002 double-blind RCT, 117 patients with alcohol dependence entering an alcohol treatment program were randomized to receive either symptom-triggered oxazepam (15–30 mg every 30 minutes) with scheduled placebo or fixed-schedule oxazepam (30 mg every 6 hours for 4 doses followed by 15 mg every 6 hours for 8 doses) with additional

PRN dosing.[2] Patients were an average of 46 years old and primarily white males. Symptom assessment was based on the CIWA-Ar. Patients were excluded if they had other medical or psychological diagnoses.[2]

Only 39% of the patients in the symptom-triggered group received any oxazepam versus 100% in the fixed-schedule group (*P*<.001). Mean oxazepam dose was 37.5 mg in the symptom-triggered group versus 231.4 mg in the fixed-schedule group (*P*<.001). Mean duration of treatment was 20 hours in the symptom-triggered group versus 62.7 hours in the fixed-schedule group (*P*<.001).[2]

One episode of seizures occurred in the symptom-triggered group. Comfort measures including health concerns, anxiety, energy, depression, and physical functioning were evaluated by survey, and no difference was measured between the groups.[2]

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What is the best way to confirm a medication abortion is complete?

EVIDENCE-BASED ANSWER

The current standard of practice to confirm the successful completion of a medical abortion is a transvaginal ultrasound confirming expulsion of the gestation sac 1 to 2 weeks after taking medications. Protocols involving urine pregnancy tests at home with phone follow-up decrease the need for in-clinic follow-up and appear to be effective in ruling out ongoing pregnancy when compared with ultrasound (SOR: **B**, RCT and case series). Follow-up with serum hCG (80% decrease from pre-abortion serum level) does not increase unplanned interventions or visits when compared with ultrasound (SOR: **B**, RCT). It is unknown if the use of these protocols (instead of ultrasound) would lead to more complications. Deciding which method to use should be based on informed and shared decision-making.

A 2014 RCT compared ultrasound with a telephone call and semiquantitative home urine pregnancy test at 2 weeks to confirm complete medication abortion in 1,433 Vietnamese women.[1] The semiquantitative urine pregnancy test (not yet available in the United States) reads multiple levels of hCG (25, 100, 500, 2,000, and 10,000 mIU/mL), and a drop of at least 1 bracket at 2 weeks was considered a complete medication abortion. Women who did not have a drop of at least 1 bracket, had an inconclusive test, or had symptoms of ongoing pregnancy were asked to return for transvaginal ultrasound (106 of 693, 15%). Women who had a drop of at least 1 bracket and no symptoms received no further follow-up (n=587), but 3 women were subsequently seen for ongoing pregnancy, retained products of conception, or uterine bleeding.

The semiquantitative urine pregnancy test had a negative likelihood ratio of 0.075; therefore, with a prevalence of ongoing pregnancy of 2.5%, a negative pregnancy test essentially ruled out ongoing pregnancy. Loss to follow-up was higher in the ultrasound follow-up group than for the phone follow-up group (8.1% vs 0.6%; risk ratio [RR] 0.07; 95% CI, 0.025–0.191). Only 15% of the telephone follow-up group required in-person visits versus 100% of the ultrasound group. This study was limited by lack of an appropriate reference standard.[1]

A 2013 RCT of 376 women from Massachusetts compared the rates of unplanned interventions or visits after medication abortion using different follow-up methods: ultrasound versus serum hCG measurements with a more than 80% decrease confirming complete abortion.[2] There was no difference in the rate of unplanned interventions or visits between the use of ultrasound versus hCG at 2 weeks (8.2% vs 6.6%; RR 1.2; 95% CI, 0.56–2.7) and 4 weeks (10.4% vs 12.7%; RR 1.2; 95% CI, 0.63–2.3).

A 2010 prospective case series of 133 women from Pittsburgh evaluated the accuracy of telephone follow-up at 1 week in combination with home high-sensitivity urine pregnancy test (sensitivity 25 mIU/mL) at 30 days to confirm complete medication abortion.[3] Ultrasound was performed only if ongoing pregnancy was suspected at the 1-week telephone call or with a positive home pregnancy test at 1 month.

No ongoing pregnancies were missed with this protocol; however, the study did not have enough power to detect this outcome. Only 23% (95% CI, 16–31) had a positive pregnancy

test that required a follow-up visit at the 30-day phone call. Overall, 64% of patients (95% CI, 56–73) never required an in-person visit.[3]

These studies were underpowered to evaluate the rare complication of ongoing pregnancy after medication abortion and if missing these rare ongoing pregnancies results in worse outcomes such as inability to have a D&C due to later gestational age, higher morbidity, and/or inability to access a clinic that performs D&C procedure at a later gestational age.

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How effective are immune modulator injections of the globe in patients with wet macular degeneration?

EVIDENCE-BASED ANSWER

For patients with wet macular degeneration, intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) immune modulators such as ranibizumab, bevacizumab, or pegaptanib can prevent loss of visual acuity and, in some cases, improve visual acuity (SOR: **A**, meta-analysis). A newer agent, aflibercept, is noninferior to ranibizumab with the advantage of bimonthly injections instead of monthly (SOR: **B**, lower quality meta-analysis).

A 2014 meta-analysis of 12 RCTs (N=5,496) including patients with "wet" or neovascular age-related macular degeneration evaluated the effectiveness of intravitreally injected pegaptanib, ranibizumab, or bevacizumab anti-VEGF treatment for prevention of loss of visual acuity.[1] The review examined the comparative effectiveness of anti-VEGF agents when given in similar doses and patterns. A key common outcome was change in visual acuity as measured by the LogMar visual scale with an Early Treatment of Diabetic Retinopathy (ETDRS) chart. Each line has 5 letters, so a change of 15 letters approximates a 3-line change on a Snellen eye chart. Ten lines on the ETDRS chart represented the difference between 20/20 and 20/200 vision.

Patients treated with ranibizumab were able to read about 18 more letters at 1 year than patients receiving sham injection or verteporfin photodynamic therapy (PDT), depending on the study (3 trials, n=1,322; mean difference [MD] 17.8; 95% CI, 16.0–19.7). Similar benefits were observed in 2 smaller studies with bevacizumab treatment; however, the controls varied within the studies, including pegaptanib injection, verteporfin PDT, steroid injection, and sham injections (2 trials, n=131 and n=28; MD 16.4 and 11, respectively; reported as significant but statistical analysis not given). Pegaptanib also showed benefit versus sham injection (2 trials, n=1,208; MD 6.7; 95% CI, 4.4–9.0). Systemic adverse events, including myocardial infarction, cerebral infarction, ischemic cardiomyopathy, or death after 1 year, were rare (<1%) and relative risk estimates were imprecise. Risk of serious adverse ocular events for these agents including endophthalmitis, uveitis, retinal detachment, and retinal or vitreous hemorrhage were also rare. For example, endophthalmitis, the most common adverse event, was reported in <1% of anti-VEGF-treated participants; no cases were reported in control groups.[1]

A newer agent, aflibercept, not included in the meta-analysis above, was evaluated in a meta-analysis of 2 RCTs (N=2,419).[2] Bimonthly aflibercept injections were shown to be noninferior to monthly ranibizumab injections in letters gained on an EDTRS chart, with mean change from baseline of 8.7 and 8.4 letters, respectively (reported as noninferior but statistical analysis not given). Additionally, bimonthly aflibercept showed a lower rate of serious ocular events than monthly ranibizumab (0.2% vs 1.1%, statistical analysis not reported).

The study authors concluded that bimonthly aflibercept may offer an equally effective, safer, and more cost-effective alternative to ranibizumab due to the fewer number of injections required.[2] EBP

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When should magnesium sulfate be initiated in patients presenting with preeclampsia without severe features?

Bottom line

In patients presenting with preeclampsia without severe features, magnesium sulfate leads to a small reduction in the risk of eclampsia, but not maternal death or stillbirth/neonatal death. Magnesium sulfate administration increases the risk of cesarean delivery and decreases placental abruption in women with undifferentiated preeclampsia, with no significant effect on other outcomes (SOR: **A**, meta-analysis of RCTs). Magnesium sulfate administration for eclampsia prophylaxis should be considered in patients with preeclampsia who develop severe features but may be withheld in the absence of severe features (SOR: **B**, guidelines citing conflicting and underpowered RCTs).

Evidence summary

A 2010 systematic review and meta-analysis of magnesium sulfate and other anticonvulsants in patients of at least 28 weeks' gestation with preeclampsia with and without severe features examined 15 high-quality RCTs (N=11,444).[1] Exclusion criteria varied, but generally excluded were patients with chronic hypertension or receiving hypertension medications, epilepsy, or cardiac or renal disease. Four studies (n=7,889) reported the incidence of eclampsia among patients with preeclampsia without severe features (BP ≥140/90 mmHg x 2, 30 minutes apart; and 24-hour proteinuria ≥300 mg/dL or ≥+1 proteinuria). Magnesium sulfate was administered as a 4- to 6-g intravenous (IV) loading dose followed by 1–2 g/h IV, or a 10-g intramuscular (IM) bolus followed by 5 g IM every 4 hours, and continued for 12 to 24 hours postpartum.

When compared with placebo or no anticonvulsant, magnesium reduced the risk of eclampsia from 1.5% to 0.66% (risk ratio [RR] 0.44; 95% CI, 0.28–0.69; number needed to treat [NNT]=100), but made no significant difference in maternal death (1 trial, n=7,468; RR 0.54; 95% CI, 0.20–1.5) or stillbirth/neonatal death (1 trial, n=6,620; RR 1.1; 95% CI, 0.91–1.2). Additional complications of magnesium sulfate administration were not analyzed separately for patients with preeclampsia without severe features. Among all patients with preeclampsia with and without severe features, magnesium sulfate reduced the risk for eclampsia compared with placebo when given after 34 weeks' gestational age (2 trials, n=6,498; RR 0.37; 95% CI, 0.24–0.59) and during the antepartum period (6 trials, n=10,109; RR 0.40; 95% CI, 0.27–0.57), but not before 34 weeks' gestational age (1 trial, n=2,412; RR 0.54; 95% CI, 0.28–1.1) or during the postpartum period (1 trial, n=1,335; RR 0.54, 95% CI, 0.16–1.8). However, magnesium administration produced an increased risk of cesarean section (absolute risk difference [ARD] 3%; RR 1.1; 95% CI, 1.0–1.1; number needed to harm=34), a reduced risk of placental abruption (2 trials, n=8,838; ARD 1.1%; RR 0.64; 95% CI, 0.50–0.83; NNT=100), and no difference in the risk of postpartum hemorrhage, admission to the special care baby unit, or neonatal intubation compared with placebo or no anticonvulsant.[1]

Recommendations from others

Both the Canadian Hypertensive Disorders of Pregnancy (HDP) Working Group[2] and the American College of Obstetricians and Gynecologists (ACOG)[3] published evidence-based guidelines for the use of magnesium sulfate in patients with preeclampsia without severe features. Both groups recommended that magnesium sulfate administration be considered in patients with preeclampsia who develop severe hypertension, headaches, visual changes, right upper quadrant/epigastric pain, platelet count <100,000 x 10^9/L, progressive renal insufficiency, or elevated liver enzymes.

The HDP Working Group called routine magnesium sulfate administration for patients with preeclampsia without severe features "controversial" due to the small increased risk of cesarean delivery and other maternal complications, as well as cost of approximately $23,000 to prevent 1 seizure.[2] ACOG suggested not universally administering magnesium sulfate to women with preeclampsia without severe features.[3] EBP

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The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of Saint Louis University, the US Air Force Medical Service, or the US Air Force at large.

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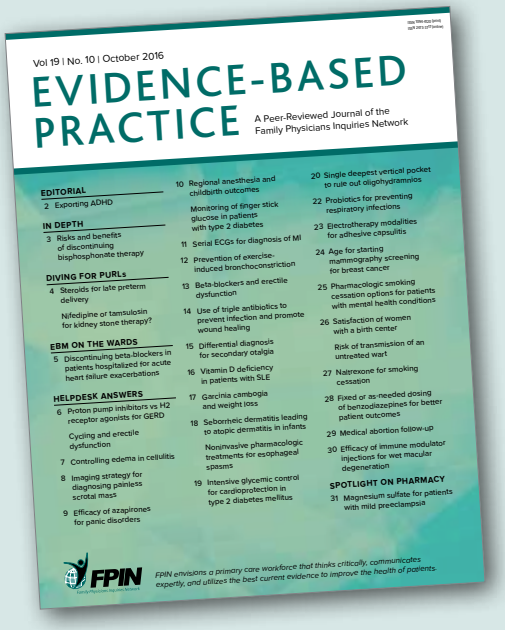

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