ISSN 1095-4120 (print)
ISSN 2473-3717 (online)

Vol 20 | No. 12 | December 2017

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

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Fractal forces

I generally like fractals—those scalable self-similar patterns that show up in math, art, and nature. The most famous one in mathematics (and on dorm posters) is the Mandelbrot set, which looks something like the Michelin Man dressed as a traditional Thai dancer. Modern artists like Jackson Pollock and Max Ernst, who tended to mess with their materials, generated visually pleasing fractal compositions relying on the physics of paint and paper years before fractals were a mathematical "thing."

But I really like fractals in nature: mountain ridges, tree branches, river channels, ice patterns, lightning bolts, and even Romanesco broccoli. They fascinate me at all scales and I could mediate on them all day long. And if you insist on being a physician about your fractals, then you have the beauty of blood vessel and airway branching to hold you in old Galen's thrall.

Conversely, however, if a little pattern is not pleasing to start with, it can be rather annoying when that pattern starts showing up at larger scales! I recently noticed this happening in the curious blindness of drug manufacturers to the toxicities of their products.

A group of researchers decided to analyze adverse-event reporting in all 185 meta-analyses published on antidepressants between 2007 and 2014.[1] In 29% of the reviews, all the meta-analysis authors were industry employees. There was some industry link (author employment, funding, or conflicts of interest) in 79% of the reviews. The meta-analyses in general tended not to discuss negative aspects of these medications, but industry-linked meta-analyses were much less likely to discuss negative effects than meta-analyses without such links (2% vs 44%; $P<.001$).

We have seen this pattern before. Other research has shown that individual RCTs sponsored by industry are also much less likely to discuss side effects than independently performed primary research. It's now clear that the same pattern of bias is erupting in meta-analyses. The biasing effect is self-similar and scales up—just like a fractal.

Natural fractals are an expression of underlying forces and mathematical principals. I can only guess at the calculus behind these patterns in industry's research reporting.

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

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What are the success rates for CPR for cardiac arrest in the community with and without rescue breathing?

EVIDENCE-BASED ANSWER

For untrained bystanders instructed by a dispatcher, compression-only cardiopulmonary resuscitation (COCPR) in adults improves survival to hospital discharge by 20% compared with cardiopulmonary resuscitation with rescue breathing (standard CPR). However, both techniques are associated with similar success if bystanders are not receiving dispatcher instruction (SOR: **A**, meta-analysis of RCTs). Standard CPR is associated with slightly higher 1-month survival rate than COCRP in mixed populations of children and adults (SOR: **B**, meta-analysis of cohort studies and single cohort study). CPR providers with prior CPR training should continue doing standard CPR, but lay providers instructed by dispatchers should do COCPR (SOR: **C**, expert opinion).

Evidence summary

A 2010 meta-analysis combined 3 large RCTs including adult patients with out-of-hospital arrest and CPR performed by bystanders and compared outcomes from dispatcher-instructed COCPR with outcomes of standard CPR (N=3,031).[1] Patients were randomized to receive instructions on COCPR or standard CPR from a dispatcher.

Survival to hospital discharge occurred in 14% of patients receiving COCPR compared with 12% of patients receiving standard CPR (risk ratio [RR] 1.2; 95% CI, 1.0–1.5; number needed to treat=41).[1]

This review also included a meta-analysis of 7 cohort studies (n=2,672) looking at the likelihood of survival in adult patients with out-of-hospital arrest based on a retrospective review of CPR technique performed by bystanders without dispatch instruction. In a pooled analysis, no benefit was found for COCPR versus standard CPR when examining a composite outcome of survival at 1 week or 1 month or being awake at 2 weeks (RR 0.99; 95% CI, 0.83–1.1).[1]

The 2015 American Heart Association (AHA) evidence-based guidelines noted that these studies were conducted in metropolitan areas where emergency medical service response times are relatively quick.[2] In areas with extended response times, prolonged periods of CPR without adequate ventilation could contribute to worsening acidosis. Because cardiac arrests in these studies are more likely to have a cardiac etiology, the AHA noted that these results may not reflect the effectiveness of COCPR in cardiac arrest from respiratory etiologies.

A 2011 cohort study looked at 1-month survival and neurologically favorable 1-month survival in all children and adults in Japan with witnessed out-of-hospital arrest over a 2-year period in which COCPR (n=20,707) or standard CPR (n=19,328) was provided by a bystander.[3] Overall, 60% of persons providing COCPR received dispatcher assistance, compared with 50% of persons providing standard CPR. The researchers adjusted for many potential confounders, including age, sex, assistance from dispatcher, initial identified cardiac rhythm, cause of cardiac arrest, use of public access automated external defibrillator, and timing of CPR and transport.

The 1-month survival rate was higher in patients receiving standard CPR than COCPR (adjusted odds ratio [OR] 1.2; 95% CI, 1.1–1.3). Neurologically favorable 1-month survival was also higher with standard CPR (adjusted OR 1.2; 95% CI, 1.0–1.4).[3]

The 2015 AHA guidelines recommended that for the lay provider who is being instructed in CPR by a dispatcher, COCPR should be provided (strong recommendation, based on limited data).[2] Lay providers who have been trained previously in CPR should provide standard CPR (moderate recommendation, based on limited data). EBP

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Induce to reduce Cesarean delivery: A protocol for obese pregnant patients

Schuster M, Madueke-Laveaux OS, Mackeen AD, Feng W, Paglia MJ. The effect of the MFM obesity protocol on cesarean delivery rates. *Am J Obstet Gynecol*. 2016; 215(4):492.e1–492.e6.

A 2016 retrospective cohort study (N=5,000) evaluated the effectiveness of an obesity protocol on the rate of Cesarean delivery for obese pregnant women. The obesity protocol consisted of screening for early gestational diabetes mellitus (GDM), recommending a weight gain of 11 to 20 pounds, measuring baseline 24-hour urine protein, obtaining serial growth scans and nonstress tests, and inducing labor by 40 weeks. The primary outcome was the rate of Cesarean deliveries. Secondary outcomes included a composite of neonatal morbidity.

The Cesarean delivery rate in obese patients postprotocol (n=1,227) was lower than preprotocol (n=846) (32% vs 42%; *P*<.0001). The number of inductions was not reported. The obese patients postprotocol had a 37% lower rate of Cesarean delivery compared with obese patients preprotocol when controlling for age, race, smoking status, preeclampsia, GDM, and intrauterine growth restriction (odds ratio 0.63; 95% CI, 0.52–0.76). No significant difference was noted in neonatal morbidity between the groups (all *P*>.05).

Limitations of this study included a retrospective design and variable adherence to the protocol by providers.

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

Bottom line: This protocol did not increase Cesarean delivery rates. However, limitations to the validity of this retrospective cohort study design included low rate of provider compliance with the protocol, changes in labor curve and arrest of dilation practices during the trial that reduced Cesarean delivery rates, and no data provided on induction rates during either time period to show potential changes in the number of inductions with the new protocol.

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Longer cervical cancer screening intervals in women over 40

Dijkstra MG, van Zummeren M, Rozendaal L, van Kemenade FJ, Helmerhorst TJ, Snijders PJ, et al. Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands. *BMJ*. 2016; 355:i4924.

This 14-year follow-up to a population-based RCT in the Netherlands studied Pap smear and human papillomavirus (HPV) cotesting versus cytology alone for detection of cervical cancer. Women 29 to 61 years old (N=43,339) were randomized to receive either a Pap smear with HPV cotesting or cytology alone. Follow-up screening occurred every 5 years; the second screening for both arms was HPV cotesting, and the third screening for both arms was cytology alone.

The primary outcome was cumulative incidence of cervical cancer and cervical intraepithelial neoplasia grade 3 or worse (CIN3+).

Cervical cancer incidence among HPV-negative and Pap/HPV-negative women from the intervention group after 3 rounds of screening was similar to that among Pap-negative women from the control group after 2 rounds of screening (risk ratio [RR] 0.97; 95% CI, 0.41–2.31). No difference was noted in CIN3+ incidence in the intervention group after 3 rounds of screening versus the control group after 2 rounds (RR 0.83; 95% CI, 0.32–2.15). In HPV-negative women aged ≥40 years, CIN3+ incidence was 72.2% lower than in women <40 (95% CI, 61.6%–79.9%; *P*<.0001).

HPV-based screening might allow more women to avoid a diagnosis of CIN3+ than cytology-based screening.

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

Bottom line: Cumulative incidence of cervical cancer and CIN3+ among HPV-negative women undergoing Pap smear and HPV cotesting after 3 rounds of screening was similar to that among cytology-negative women screened with only Pap smear after 2 rounds. Increasing HPV-based screening intervals to 10 years for women >40 years of age may be safe, but implementation of such a change may be problematic as this significant deviation from the standard of care likely requires more cumulative evidence before recommending. EBP

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Should pregnant women with a history of LEEP have cervical length screening in the second trimester?

CASE

A 27-year-old primigravida presents for a follow-up visit at 20 weeks. She underwent a loop electrosurgical excision procedure (LEEP) 2 years ago for cervical intraepithelial neoplasia grade 2 (CIN2). You consider whether to order a transvaginal ultrasound to assess cervical length, which might alert you to an increased risk of preterm delivery.

Bottom line

Evidence is insufficient to support screening for cervical length in women with a history of LEEP.

Review of the evidence

A short cervical length, commonly defined as <25 mm, predicts preterm birth. The potential benefit of assessing cervical length with transvaginal ultrasound in women with a history of LEEP is indirect.

Among asymptomatic women who screen positive for short cervical length during the second trimester, vaginal progesterone was found to decrease the risk of preterm birth. A 2016 systematic review and meta-analysis of 5 trials (N=974) found that treating asymptomatic women with singleton pregnancies and no history of preterm delivery who screen positive for a cervical length of ≤25 mm before 24 weeks with vaginal progesterone was associated with a decreased risk of preterm birth versus placebo (18.1% vs 27.5%; relative risk [RR] 0.66, 95% CI, 0.52–0.83).[1]

No difference was noted between groups in the rate of maternal adverse events (13.8% vs 13.4%) or discontinuation of therapy due to adverse events (2.6% vs 2.6%). The potential harms to screening for cervical length include maternal anxiety and inconvenience, and increased cost of interventions.[1]

In a 2014 retrospective cohort study at a center with a universal protocol for cervical length screening between 18 and 24 weeks' gestation, 6.5% (n=30 of 460) of women with a prior cervical excision procedure had a cervix <30 mm versus 1.5% (n=93 of 6,209) of women without a history of cervical excision (*P*<.001).[2] The mean cervical length was 42 mm in the group with prior cervical excision compared with 45 mm in the group without (*P*<.001).

A recent systematic review and meta-analysis of 71 studies assessing more than 6 million women found LEEP was associated with a higher risk of preterm birth (RR 1.56; 95% CI, 1.36–1.79).[3] Even taking into account that women with CIN had an increased risk of preterm birth compared with the general population (RR 1.24; 95% CI, 1.14–1.35), women with CIN plus a history of LEEP still had an increased risk of preterm birth (RR 1.34; 95% CI, 1.10–1.64). Risk of preterm birth increased with greater excisional depths and volumes, and among women who had multiple LEEPs.

Recommendations from others

ACOG and the Society for Maternal-Fetal Medicine recommend routine vaginal ultrasound screening in women with a history of preterm birth.[4,5] However, evidence is insufficient to support additional screening for women with a previous electrosurgical procedure (LEEP) or cold knife cone for cervical dysplasia.[6]

Although universal screening is probably cost effective, a recent prospective observational cohort study of primigravid women reported that cervical length measurement was a poor screening test with low sensitivity for spontaneous preterm birth.[7]

CASE WRAP-UP

Based on insufficient evidence, you had a discussion focused on shared decision-making, and she opted not to screen. EBP

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Are balloon Foley catheters effective when used alone for cervical ripening?

EVIDENCE-BASED ANSWER

Foley catheters alone are as effective as Foley catheters with oxytocin in effecting delivery within 24 hours—with similar rates of Cesarean delivery, uterine hyperstimulation, and postpartum hemorrhage—although the addition of oxytocin may be more effective in multiparous women. Foley catheter treatment outcomes are similar to prostaglandin E2 ripening in rates of vaginal delivery, instrumental delivery, and Cesarean delivery. Single-balloon catheters are equivalent to double-balloon catheters in time to delivery, but double-balloon catheters may increase the rate of operative deliveries and other adverse events (SOR: **B**, single RCTs)

A 2008 RCT involving 200 pregnant women examined the effect of cervical ripening with transcervical Foley catheters with or without oxytocin on delivery within 24 hours.[1] Inclusion criteria were women presenting for induction with singleton pregnancies in a cephalic position with a gestational age of at least 23 weeks. On average, patients were 28 years old, at 39 weeks' gestation, and had a Bishop score of 3.3. Both arms of the study had similar numbers of multiparous and nulliparous women. Oxytocin was administered according to a protocol and titrated to achieve acceptable contraction rates without tachysystole.

No difference was noted in the proportion of deliveries in 24 hours between Foley catheter alone or Foley catheter plus oxytocin (relative risk [RR] 1.1; 95% CI, 0.86–1.4). Nor was there a difference in rates of Cesarean deliveries, duration of ripening, or time to delivery. When the results were stratified by parity, no difference was noted in outcomes in nulliparous women, but among the multiparous subgroup (n=59) more deliveries in 24 hours occurred in the Foley catheter plus oxytocin group (RR 1.3; 95% CI, 1.1–1.7; number needed to treat=5) but no difference was noted in the proportion of vaginal deliveries or Cesarean deliveries in 24 hours. Complication rates (chorioamnionitis, postpartum hemorrhage, or uterine hyperstimulation) were similar for both subgroups.[1]

A 2011 open-label RCT in the Netherlands compared the effectiveness and safety of induction of labor with a Foley catheter versus vaginal prostaglandin E2 gel.[2] Women were at term (N=824) with singleton pregnancies in cephalic presentation, intact membranes, unfavorable cervix, and no prior Cesarean delivery.

In the Foley group, compared with the prostaglandin group, no differences were noted in vaginal deliveries (66% vs 67%; *P*=.94), vaginal instrumental deliveries (11% vs 13%; *P*=.32), or Cesarean deliveries (23% vs 20%; *P*=.38). Fewer neonates were admitted to the neonatal ward after induction with a Foley compared with prostaglandins (12% vs 20%; *P*=.0019).[2]

This report also included a meta-analysis of this trial and an additional 2 RCTs comparing induction with a Foley catheter with prostaglandin E2 gel and found no difference in Cesarean delivery rate (3 trials, n=1,441; risk ratio [RR] 1.0; 95% CI, 0.8–1.3). However, hyperstimulation and postpartum hemorrhage occurred less often after induction with Foley catheter than after prostaglandin (3 trials, n=1,441; odds ratio [OR] 0.44; 95% CI, 0.21–0.91 and OR 0.60; 95% CI, 0.37–0.95, respectively).[2]

A 2011 RCT assessed the efficacy of a single-balloon catheter compared with a double-balloon catheter in 293 women with unfavorable cervices undergoing induction of labor.[3] The women had a live singleton gestation in cephalic presentation, intact membranes, and a Bishop score of 6 or less.

No difference was noted between single- and double-balloon catheters for delivery time (18.8 vs 19.4 hours; *P*=.8). More women induced with a double-balloon catheter compared with a single balloon required operative delivery by vacuum assist or Cesarean (26% vs 14%; *P*=.02). Composite adverse events, including intrapartum fever, malpresentation, and cord prolapse, were higher in the double-balloon group than in the single-balloon group (7.4% vs 1.4%; *P*=.02).[3]

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What is the best therapy for anal fissures?

EVIDENCE-BASED ANSWER

Surgical management is consistently superior to topical diltiazem or glyceryl trinitrate for chronic anal fissure (SOR: **A**, systematic review and meta-analysis) and perhaps also for acute anal fissure (SOR: **C**, small cohort study). Among medical therapies, diltiazem 2% ointment and glyceryl trinitrate 0.2% ointment are equally effective, but diltiazem has a 30% lower recurrence rate and a 60% lower incidence of headache (SOR: **A**, systematic review of RCTs).

A 2012 systematic review (15 RCTs, N=979) compared surgical intervention with any medical therapy for patients with chronic anal fissure.[1] Chronic anal fissure was defined as symptoms for more than 4 weeks or the presence of anatomical changes characteristic of chronic fissure. The nonsurgical groups received topical glyceryl trinitrate, topical diltiazem, or botulinum toxin in the meta-analysis. Doses and frequencies of the medical therapies varied across studies, and surgical management was lateral internal sphincterotomy in all but 1 trial. The studies were of good quality and moderately heterogeneous in design (I^2=62%), with 1 study including pediatric patients and another single study including acute anal fissure. Average length of follow-up was 2 months.

The crude rate of nonhealing was 10.8% in the surgery group and 46.7% in the medical group (odds ratio [OR] 0.11; 95% CI. 0.0–0.23).[1]

A 2010 prospective cohort study compared lateral internal sphincterotomy with topical nitroglycerine ointment in 340 patients with acute or chronic anal fissure.[2] Chronic fissure was defined in this study as the presence of anatomical changes associated with chronicity. Patients were divided into acute and chronic groups, with the acute anal fissure group given nitroglycerin first and surgery if they did not heal. The chronic group was given a choice of surgery or medical therapy, and 30% chose medical therapy.

The healing rate for nitroglycerine as the initial therapy was 63% in the acute group and 49% in the chronic group. The 70% of patients in the chronic group who opted for surgery were all declared healed, as well as the surgical patients who had failed nitroglycerine therapy (excluding patients lost to follow-up). A significant improvement in the healing rate was noted with sphincterotomy compared with nitroglycerine (OR 345; *P*=0.000). The dose of nitroglycerine was not specified in the methods, and 7.64% of patients were lost to follow-up at some point during the study.

A 2013 systematic review (7 RCTs, N=481) compared the effectiveness of topical diltiazem 2% ointment with topical nitroglycerine 0.2% ointment for patients with chronic anal fissure.[3] The 7 trials had significant heterogeneity (I^2=79%) and no unified definition of chronic anal fissure.

Both treatments were equally effective for initial healing (RR 1.1; 95% CI, 0.9–1.34). The diltiazem ointment was associated with a lower risk of recurrence (RR 0.68; 95% CI, 0.52–0.89) and a lower incidence of headache (RR 0.39; 95% CI, 0.24–0.66).[3]

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Does amitriptyline prophylaxis decrease the frequency of migraines?

EVIDENCE-BASED ANSWER

Yes, by most measures. Amitriptyline leads to large reductions in the frequency of migraines compared with placebo over 24 weeks (SOR: **B**, meta-analysis of conflicting RCTs). Amitriptyline leads to 1 less migraine per month compared with placebo at 12 weeks and about twice as many patients reporting a 50% reduction in headache days (SOR: **B**, RCT).

A 2015 meta-analysis of 179 RCTs (N=5,831) evaluated the effectiveness of various drug therapies, including amitriptyline, for prophylaxis of episodic migraines in adults

with migraine headaches.[1] Placebo-controlled trials with intention-to-treat analysis of at least 4 weeks' duration were included. Four RCTs (n=677) studied changes in migraine frequency in patients who received amitriptyline 60 to 100 mg daily versus placebo. Change in migraine frequency was measured in patient diaries using different scales, so results were reported as standardized mean differences (SMD).

Amitriptyline led to a moderate decrease in episodic migraines at 4 weeks (2 studies, n=103; SMD –0.57; 95% CI, –0.92 to –0.23) and a large decrease at 24 weeks (2 studies, n=574; SMD –1.2; 95% CI, –1.7 to –0.82) compared with placebo. Adverse events including dry mouth and fatigue were more common in the amitriptyline group (risk ratio [RR] 1.5; 95% CI, 1.3–1.7; number of pooled studies and patients not reported).[1]

A 2011 RCT enrolled 391 adult patients with at least 2 migraine headaches per month to compare the effect of amitriptyline (25 mg daily, n=194) versus placebo (n=197) on migraine frequency over 20 weeks.[2] This RCT was the largest study included in the 2015 systematic review described above, so is being detailed separately. Patients were 18 to 70 years old with at least 2 migraine headaches per month in addition to other types of headaches. Reduction in migraine frequency was defined as the percentage of patients who experienced fewer migraines compared with baseline. During the first 4 weeks of the study, all patients received placebo to establish baseline migraine frequency. During weeks 5 to 20, the intervention group received amitriptyline 50 mg daily for 1 week, 75 mg daily the next week, and 100 mg daily for the subsequent 13 weeks as tolerated, and the control group received placebo.

A greater percentage of patients taking amitriptyline had fewer migraines compared with patients taking placebo at 8 weeks (42% vs 37%; *P*=.02, number needed to treat=20), but not at 12, 16, or 20 weeks. High dropout rates were a limitation of this study, with 48% of patients in the amitriptyline group and 54% of patients in the placebo group dropping out before 20 weeks.[2]

A 2016 RCT of 178 adult patients with at least 3 migraine attacks per month or 4 migraine headache days per month compared the efficacy of amitriptyline 25 mg daily (n=59), melatonin 3 mg daily (n=60), or placebo (n=59) at reducing the number of migraine headache days per month compared with baseline over 12 weeks.[3] The patients recorded headaches with symptoms lasting at least 30 minutes in a journal reviewed by a neurologist who was unaware of patient treatment assignment and who determined if the headache was or was not a migraine. A secondary outcome was the number of responders, defined as patients with more than a 50% reduction in headache days. Patients were randomized after a 4-week run-in period to establish baseline migraine frequency.

Amitriptyline reduced the number of migraine headache days per month by 1.1 more days than placebo at 12 weeks (*P*<.05). At 12 weeks, the responder rate in the amitriptyline group was 39% compared with 20% in the placebo group (*P*<.01). At 12 weeks, no significant difference was noted in reduction of headache days per month between the melatonin (2.7 days) and amitriptyline (2.2 days) groups, but melatonin was superior to amitriptyline for the number of responders (54% vs 39%; *P*<.05). The most common adverse events in the amitriptyline group were sleepiness (41%) and dry mouth (10%).[3]

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In geriatric patients, does regular exercise delay onset of dementia compared with no exercise?

EVIDENCE-BASED ANSWER

Physical activity and midlife fitness is associated with a lower risk of dementia (SOR: **B**, meta-analysis and cohort study). Multidimensional lifestyle modification, including exercise, minimally reduces risk of cognitive decline (SOR: **B**, RCT).

A 2015 meta-analysis of 9 prospective studies (N=20,326) evaluated the effect of physical activity level on onset of Alzheimer's disease (AD) over 4- to 7-year follow-up.[1]

Participants included adults 65 years or older without known dementia at the beginning of the study. Assessment of physical activity varied among studies; most studies used questionnaires based on frequency, duration, or intensity. AD was diagnosed using standardized clinical criteria.

The risk of developing AD was lower in adults who were physically active compared with adults who were not (fixed-effects relative risk 0.61; 95% CI, 0.52–0.73). Most studies relied on self-reported physical activity level, possibly underestimating risk reduction.[1]

A 2013 prospective cohort study of adults (age at enrollment <56 years, average age 50 years) evaluated the effect of cardiorespiratory fitness level on later incidence of dementia (N=19,458).[2] Exclusion criteria included myocardial infarction, stroke, Medicare enrollment due to disability before age 65, or dementia before age 65. Mean follow-up was 24 years. Participants were stratified into 5 metabolic equivalent of task (MET) groups based on maximal treadmill exercise time. Dementia was determined based on ICD-9 coding.

Patients with a higher fitness level (MET >11) at enrollment had a lower risk for dementia than patients with a baseline MET of 8.4 (hazard ratio 0.64; 95% CI, 0.54–0.77).[2]

A 2015 double-blinded RCT studied the effect of a multidomain intervention on prevention of cognitive decline in 1,260 at-risk adults.[3] At-risk adults were identified using validated predictive tools, including the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) and Consortium to Establish a Registry for Alzheimer's Disease (CERAD, a comprehensive battery of clinical, behavioral and neuropathological tests) scales. Participants received a multidomain intervention (diet, exercise, cognitive training, individualized vascular risk monitoring, and counseling) or routine care. Exercise included strength training 1 to 3 times per week and aerobic activities with balance training 2 to 5 times per week. Change in cognitive function was assessed at 0, 12, and 24 months using the neuropsychological test battery (NTB) z-scores. NTB is a validated measure including 9 component tests of cognitive and executive functional decline.

At 24 months, the intervention group had less decline than the control group in overall cognitive function (mean difference [MD] in NTB z score 0.022; 95% CI, 0.002–0.042, effect size 0.127), executive function (MD 0.027; 95% CI, 0.001–0.052; effect size 0.129), and processing speed (MD 0.030; 95% CI, 0.003–0.057, effect size 0.129), but not memory (MD 0.015; 95% CI, –0.017 to 0.048). An effect size of 0.2 is considered small.[3]

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Does induction of labor before 41 weeks improve outcomes in pregnancies complicated by obesity?

EVIDENCE-BASED ANSWER

Induction of labor before 41 weeks does not improve outcomes in nulliparous pregnancies complicated by obesity, and increases the risk of Cesarean delivery and its associated risks, including neonatal intensive care unit (NICU) admission rates (SOR: **B**, cohort studies). Labor induction and scheduled Cesarean delivery have similar maternal and neonatal outcomes (SOR: **B**, cohort studies). Extreme obesity (weighing >275 lb at delivery) triples the risk of requiring Cesarean delivery (SOR: **B**, cohort studies).

A 2014 retrospective cohort study compared elective induction of nulliparous, term, obese women (n=60) with an unfavorable cervix with expectant management (n=410) on maternal and neonatal outcomes.[1] Inclusion criteria were nulliparity, gestational age of at least 39 weeks, singleton in vertex presentation, with documented cervical exam between 38 and 38.9 weeks with modified Bishop score <5, and a body mass index (BMI) of 30 or more at delivery. Exclusion criteria included women with medical comorbidities, such as chronic hypertension. The mean age of patients in the study was 22 years, and the mean BMI was 36. The most common indications for delivery in the expectantly managed group

were spontaneous labor (37%) and spontaneous rupture of membranes (33%). Only 9% of women in the expectant management group were induced for postdates.

The rate of Cesarean delivery was higher in the elective induction group than the expectant management group (40% vs 26%; *P*=.022). Other maternal outcomes, including operative vaginal delivery, chorioamnionitis, and postpartum hemorrhage, were similar. The NICU admission rate was significantly higher in the elective induction group (18% vs 6.3%; *P*=.001), whereas birthweight, rates of umbilical artery pH less than 7.0, and rates of Apgar less than 7 at 5 minutes were similar. No neonatal deaths occurred in either group.[1]

A 2014 retrospective cohort study compared maternal and neonatal outcomes of induction of labor (n=399) versus planned Cesarean delivery (n=262) in obese women.[2] Inclusion criteria included women with BMI ≥40, singleton pregnancy, and term gestation from 37 to 41 weeks of gestation. Maternal morbidity outcomes included, but were not limited to, death, infection, postpartum hemorrhage, other operative complications, and thromboembolic events. Neonatal morbidity outcomes included stillbirth, hypoxic ischemic encephalopathy, NICU admission, mechanical ventilation, sepsis, respiratory distress syndrome, necrotizing enterocolitis, and death, among others. Average age was 28 years in the induction group and 29 years in the Cesarean group; 69% of the women in both groups had BMI between 40 and 50, with the remaining 31% >50; and average gestational age at delivery was 38.6 weeks in both groups.

No significant difference was noted in the maternal morbidity composite (adjusted odds ratio [aOR] 0.98; 95% CI, 0.6–1.8) or in the neonatal morbidity composite (aOR 0.81; 95% CI, 0.4–1.8) between the labor induction group and the scheduled Cesarean group. Of the 399 women undergoing induction of labor, 258 (65%) had cervical ripening and 163 (41%) ultimately had Cesarean delivery.[2]

A 2013 retrospective cohort study of 357 pregnant women conducted between 2008 and 2010 at Duke University Hospital evaluated the predictors of Cesarean delivery in extremely obese women (weighing >275 lb at delivery) delivering at >34 weeks' gestation with singleton pregnancies.[3] Mean gestational age at delivery was 38.5 weeks for the vaginal group and 38.7 weeks for the Cesarean group (*P*=.452). Exclusion criteria were multiple gestation, pregnancy complicated by congenital abnormalities, or intrauterine fetal demise.

Overall, nulliparous women, compared with parous women, had an increased risk for Cesarean delivery with a 10-kg/m^2 increase in BMI (odds ratio [OR] 3.5; 95% CI, 1.5–9.1). Similar risk was not found for multiparous women. With inductions for any indication, the rate of Cesarean delivery for extremely obese women was higher than for nonobese nulliparous women (OR 3.0; 95% CI, 1.0–10).[3]

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Do SGLT-2 inhibitors improve cardiovascular outcomes in patients with type 2 diabetes?

EVIDENCE-BASED ANSWER

Yes. In patients with type 2 diabetes, treatment with sodium glucose cotransporter 2 (SGLT2) inhibitors lead to a 30% to 40% decreased risk of cardiovascular death and a 30% decreased risk death from any cause. They also lead to reductions in other major adverse cardiovascular outcomes including new-onset heart failure and hospitalization due to heart failure (SOR: **A**, meta-analyses of RCTs, heavily influenced by 1 RCT).

A 2016 systematic review and meta-analysis evaluating the effects of SGLT2 inhibitors on cardiovascular events in adults with type 2 diabetes included 57 RCTs (n=33,385) and 6 regulatory submissions (n=37,525).[1] The 57 RCTs included 47 placebo-controlled trials, 4 trials with an active comparator, and 6 trials with both a placebo and active comparator. The mean age of participants ranged from 48 to 68 years and proportions of women in the studies ranged from 14% to 56%.

TABLE

Meta-analysis of efficacy of SGLT2 inhibitors versus placebo on cardiovascular outcomes[1]

Outcome	SGLT2 inhibitor	No. of patients	Relative risk (95% CI)
All-cause mortality	Canagliflozin, dapagliflozin, empagliflozin	29,507	0.7 (0.6–0.8)[d]
Cardiovascular death	Canagliflozin, empagliflozin	16,743	0.6 (0.5–0.8)[d]
Heart failure	Empagliflozin	7,020	0.7 (0.5–0.9)[d]
MACE[a]	Canagliflozin, dapagliflozin, empagliflozin, ipragliflozin[c]	27,078	0.8 (0.8–1.0)[d]
MACE plus[b]	Canagliflozin, dapagliflozin, empagliflozin	29,690	0.9 (0.8–1.0)[d]
Unstable angina	Canagliflozin, empagliflozin	16,743	1.0 (0.7–1.2)
Nonfatal MI	Canagliflozin, empagliflozin	16,743	0.9 (0.7–1.1)
Nonfatal stroke	Canagliflozin, empagliflozin	16,743	1.3 (1.0–1.7)[d]

[a]Defined as cardiovascular death, nonfatal MI, or nonfatal stroke.
[b]MACE with hospital admission for unstable angina.
[c]Ipragliflozin is not approved in the United States.
[d]Statistically significant results.

MACE=major adverse cardiovascular events; MI=myocardial infarction; SGLT2=sodium glucose cotransporter 2.

The SGLT2 inhibitors included in the pooled analyses were canagliflozin, dapagliflozin, empagliflozin, and ipragliflozin (not available in the United States); dosage regimens were not reported. Many outcomes included data for only 1 or 2 specific drugs (see **TABLE**).

SGLT2 inhibitors reduced the risk of death from cardiovascular causes and death from any cause compared with placebo. SGLT2 use was also associated with a reduction in major adverse cardiovascular events (MACE, defined as cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal stroke), the composite outcome of MACE and hospital admission for unstable angina (MACE plus), and heart failure hospitalizations. SGLT2 inhibitors did not protect against nonfatal MI or hospital admission for unstable angina when these outcomes were assessed separately; furthermore, SGLT2 inhibitors increased the risk of nonfatal stroke compared with placebo.[1]

There was no significant heterogeneity observed in outcomes for different SGLT2 inhibitors. The risk of bias was assessed as low for all analyses. For all outcomes, the authors noted that the results of the meta-analysis were largely driven by studies using empagliflozin, which contributed more than 70% of all cardiovascular events in the meta-analysis.[1]

A second systematic review and meta-analysis, also from 2016, also examined the effects of SGLT2 inhibitors on cardiovascular events in adults with type 2 diabetes.[2] The authors selected 43 RCTs (n=33,370) comparing SGLT2 inhibitors against either placebo (38 trials, n=28,954) or active treatment (5 trials, n=4,416). Twenty-two trials (n=20,954) had been included in the systematic review detailed above. The mean age ranged from 53 to 69 years and proportions of women ranged from 23% to 56%. The SGLT2 inhibitors studied were canagliflozin, dapagliflozin, empagliflozin, and ipragliflozin.

Similar to the other systematic review, SGLT2 inhibitor treatment reduced the risk of all-cause death (30 trials, n=27,028; relative risk [RR] 0.7; 95% CI, 0.6–0.8), cardiovascular death (12 trials, n=14,900; RR 0.7; 95% CI, 0.5–0.8), and new-onset heart failure (23 trials, n=21,188; RR 0.7; 95% CI, 0.5–0.8). However in this meta-analysis, SGLT2 inhibitors reduced the risk of MI (29 trials, n=17,381; RR 0.8; 95% CI, 0.7–1.0) but had no effect on stroke risk (22 trials, n=21,908; RR 1.2; 95% CI, 0.9–1.5).[2]

This meta-analysis was also heavily influenced by the same, single RCT mentioned previously. When the authors excluded this RCT and repeated the meta-analysis, the effect of SGLT2 inhibitors on the risk of MI remained significant

(RR 0.6; 95% CI, 0.4–0.9); however, the relative risks for all-cause death and cardiovascular death were no longer statistically significant (RR 0.8; 95% CI, 0.6–1.2 and RR 1.4; 95% CI, 0.7–2.7, respectively).[2]

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What is the best empiric antibiotic treatment regimen in adults hospitalized with community-acquired pneumonia?

EVIDENCE-BASED ANSWER

Fluoroquinolone monotherapy or a beta-lactam combined with a macrolide are both associated with lower 30-day mortality rates than beta-lactam monotherapy in adults hospitalized with community-acquired pneumonia (CAP) (SOR: **B**, systematic review of observational studies and RCTs). Macrolide use is associated with reduced mortality compared with nonmacrolide therapies in critically ill adults (SOR: **B**, systematic review of observational studies). Either a respiratory fluoroquinolone or a beta-lactam plus macrolide should be used for hospitalized patients outside of the intensive care unit (ICU), and a beta-lactam plus either a fluoroquinolone or azithromycin should be used for patients in an ICU (SOR: **C**, expert opinion).

A 2016 systematic review of 9 observational studies (N=61,442) and 2 noninferiority RCTs (N=2,863) examined the effectiveness of either beta-lactam plus macrolide therapy (8 observational study and 2 RCTs) or fluoroquinolone monotherapy (3 observational studies and 1 RCT) compared with beta-lactam monotherapy in adults hospitalized with radiographically confirmed CAP.[1]

The observational studies included 4 retrospective and 3 prospective cohort trials, as well as 2 secondary analyses of combined cohort and clinical trial data. Studies assessed mortality at varying follow-up intervals (1, 3, or 6 months as well as in-hospital and end of therapy); 1-month mortality was the most common interval (5 studies). The reviewers did not perform a meta-analysis.[1]

Of 8 observational studies (n=59,374) comparing mortality with beta-lactam plus macrolide therapy against beta-lactam monotherapy, 6 favored combination therapy (n=57,069; odds ratios [OR] ranged from 0.3 [95% CI, 0.2–0.6] to 0.7 [95% CI, 0.6–0.9]), while 2 (n=2,305) found no significant difference between the 2 treatments. All 3 observational studies (n=29,695) comparing mortality with fluoroquinolone monotherapy to beta-lactam monotherapy favored fluoroquinolone treatment; ORs ranged from 0.6 (95% CI, 0.4–0.9) to 0.7 (95% CI, 0.6–0.9). The 2 RCTs found no significant differences in mortality among the 3 therapies.[1]

In 2014, a systematic review of 28 observational studies examined macrolide versus nonmacrolide therapy in 9,850 critically ill (ie, admitted to an ICU) adult patients with CAP.[2] Macrolides varied from study to study, but compared the same drug at standard dosing for different durations of treatment within each study. The primary outcome was mortality, either in the hospital or in the ICU, or at 28 or 30 days.

Macrolide use was associated with a 3% lower mortality than nonmacrolide treatment (21% vs 24%, respectively; 28 studies, n=9,850; risk ratio 0.82; 95% CI, 0.70–0.97).[2]

Both systematic reviews were limited by the lack of RCT data and reliance on observational studies, many of which were retrospective. Also, several trials did not contain information about patient demographics, etiologic agents, and other confounding variables. Only 1 study (N=2,950) was included in both systematic reviews.

The Infectious Diseases Society of America and the American Thoracic Society 2007 evidence-informed but consensus-based guidelines on the management of CAP in adults recommend treating non-ICU inpatients with either a respiratory fluoroquinolone or a beta-lactam plus macrolide (strong recommendation; evidence from well-conducted RCTs).[3] Patients in an ICU with CAP should receive a beta-lactam plus either a fluoroquinolone (strong recommendation; evidence from well-conducted RCTs) or azithromycin (strong recommendation; evidence from well-designed, controlled trials without randomization, including

cohort, patient series, and case-control studies). According to the IDSA, an update to these guidelines is projected to be published in Spring 2018.

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Is clopidogrel plus aspirin superior to aspirin alone for primary prevention of cardiovascular outcomes among patients with multiple risk factors?

EVIDENCE-BASED ANSWER

No, clopidogrel plus aspirin (ASA) is not better than ASA alone for primary prevention of cardiovascular outcomes among patients with multiple risk factors, and this combination therapy increases the risk of bleeding (SOR: **B**, RCT). ASA alone is recommended for primary prevention in patients aged 50 to 59 years old with a 10-year risk of cardiovascular disease (CVD) of 10% or more and a low bleeding risk; ASA is recommended selectively in patients 60 to 69 years old (SOR: **C**, expert opinion).

A 2006 multicenter, double-blind RCT of 15,603 patients with multiple cardiovascular risk factors compared ASA alone versus dual antiplatelet therapy (DAPT) with ASA plus clopidogrel for reducing cardiovascular outcomes.[1] Patients were 45 years old or older with at least 1 of the following conditions: multiple atherothrombotic risk factors (smoking, diabetes, hypertension, hyperlipidemia, and heart failure) or documented coronary disease, cerebrovascular disease, or symptomatic peripheral arterial disease. Patients were excluded if they were taking oral antithrombotic medications or NSAIDS, required clopidogrel, or were scheduled for revascularization.

A post hoc analysis of this study evaluated primary prevention in a subgroup of 2,289 patients with cardiovascular risk factors but no known CVD.[2] Patients took low-dose ASA (75–162 mg/d) or DAPT (low-dose ASA and clopidogrel 75 mg/d). The outcomes examined were cardiovascular death, all-cause mortality, myocardial infarction, stroke, and hospitalization. The DAPT group and ASA group were similar at baseline except for significantly more patients with diabetes in the DAPT group (88% vs 86% respectively; *P*=.048).

After a median follow-up of 28 months, ASA and DAPT had similar rates of cardiovascular mortality (1.8% vs 3.0%; *P*=.07), overall mortality (3.2% vs 4.4%; *P*=.18), myocardial infarction (1.5% vs 1.7%; *P*=.76), stroke (1.9% vs 2.4%; *P*=.42), and hospitalization (6.5% vs 7.1%; *P*=.54). The DAPT group had a higher rate of minor bleeding (33% vs 19%; *P*<.001) and any bleed (35% vs 21%; *P*<.001), but no differences in moderate (2.2% vs 1.3%; *P*=.54) or severe (2.0% vs 1.4%; *P*=.27) bleeding.[2]

In 2016, the US Preventive Services Task Force (USPSTF) made evidence-based recommendations on use of ASA for primary prevention of CVD based on age.[3] ASA was recommended in patients 50 to 59 years old with a 10-year risk of CVD of 10% or more with no increased bleeding risk and a life expectancy of at least 10 years (Grade B: recommended, moderate benefit). For patients 60 to 69 years old and a 10-year risk of CVD of 10% or more, an individualized approach to ASA was recommended (Grade C: selectively recommended, small benefit). The USPSTF stated evidence was insufficient for ASA use in patients younger than 50 or older than 70 (Grade I: insufficient evidence to determine benefit). The guideline made no mention of clopidogrel.

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Are topical NSAIDs effective in decreasing pain from acute musculoskeletal injuries?

EVIDENCE-BASED ANSWER

Yes. Topical NSAIDs are up to 60% more likely to reduce pain from acute musculoskeletal injuries by 50% at day 7 than placebo (SOR: **A**, meta-analysis of RCTs). Topical salicylates are nearly twice as likely to decrease pain scores by 50% at day 7 compared with placebo, but may have increased systemic and local adverse reactions (SOR: **B**, meta-analysis of poor quality RCTs).

In 2015, a meta-analysis of 61 RCTs (N=9,001) reviewed topical NSAID use among patients with acute musculoskeletal pain.[1] Acute musculoskeletal pain was defined as pain for less than 3 months, but most patients had pain related to sports injuries of less than 48 hours' duration. Patients were older than 16 years (median age 25–57). Patients were treated with a topical NSAID or a placebo, which came in creams, gels, sprays, or plasters and were applied from 1 to 6 times daily for 5 to 21 days, with most treated for 14 days. Topical NSAID dosages were not reported consistently. Treatment success was defined as participant-reported reduction in pain of at least 50% at 7 days, as measured by a visual analog scale, numerical rating scale, or equivalent measure.

Diclofenac, ibuprofen, ketoprofen, piroxicam, and indomethacin were more likely than placebo to reduce pain by 50% at day 7 (see **TABLE**). No difference was noted in local (erythema and pruritus) or systemic adverse events between topical NSAIDs and placebo.[1]

A 2014 meta-analysis (17 RCTs, N=1,368) investigated the use of topical salicylates for acute and chronic musculoskeletal pain in adults older than 16 years.[2] Musculoskeletal pain was primarily from injuries, including sprains, strains, and acute low back pain. Patients were treated with a salicylic acid derivative versus placebo. The salicylic acid derivatives (dosages not reported) and placebo were formulated into creams, gels, or sprays, and applied directly to the affected area 2 to 4 times daily for 3 to 14 days for acute pain. Clinical success at 7 days was defined as 50% reduction in pain.

In acute conditions, topical salicylates were superior to placebo (see **TABLE**). Compared with placebo, topical salicylates showed a significant increase in both systemic and local adverse reactions (11 RCTs, n=984; RR 1.6; 95% CI, 1.2–2.0; NNH=17; and 10 RCTs, n=869; RR 2.2; 95% CI, 1.1–4.1, NNH=31; respectively). However, after removing 1 to 2 low-quality studies from the respective analyses, no statistically significant difference remained between salicylate and placebo for systemic or local adverse events. Most of the studies had biases such as small size, failure to report baseline pain intensity, poorly defined outcomes, and failure to explicitly report numbers of participants who withdrew, were excluded, and were lost to follow-up.[2] EBP

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TABLE

Meta-analyses of topical NSAIDs or salicylates vs placebo for treatment of acute musculoskeletal pain

Drug	No. of pooled RCTs	No. of participants	RR for a 50% reduction in pain after 1 week (95% CI)	NNT
Diclofenac[1]	10	2,050	1.6 (1.5–1.7)	4
Ibuprofen[1]	5	436	1.6 (1.3–2.0)	5
Ketoprofen[1]	7	683	1.6 (1.4–1.8)	4
Piroxicam[1]	3	504	1.5 (1.3–1.7)	5
Indomethacin[1]	3	341	1.3 (1.0–1.6)	9
Benzydamine[1]	3	193	1.2[a] (0.96–1.4)	NA
Salicylates[2]	4	324	1.9 (1.5–2.5)	4

[a]Nonsignificant difference.
NA=not available; NNT=number needed to treat; RR=relative risk.

How effective is bupropion augmentation for SSRI-induced sexual dysfunction?

Bottom line

Bupropion does not result in a significant improvement in overall sexual function in patients with selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction (SOR: **B**, small RCTs). Bupropion may slightly increase sexual desire (SOR: **C**, small RCT).

Evidence summary

A 2005 double-blinded RCT randomized 41 patients with sexual dysfunction (24 women and 17 men, 18–60 years old) on a fixed, therapeutic SSRI dose, to either 150 mg/d bupropion sustained-release (SR) or placebo over 6 weeks.[1] Patients were taking 20 mg/d fluoxetine, paroxetine, or citalopram or 50 mg/d sertraline for at least 6 weeks, with an Arizona Sexual Experiences Scale (ASEX) score of a least 15 out of 30. ASEX is a validated 5-item questionnaire based on a 6-point Likert scale scored from 5 to 30, with higher scores demonstrating greater sexual dysfunction (decreased libido, arousal, and orgasms). Significant improvement of sexual function with bupropion was defined as a 50% reduction of ASEX scores.

After 6 weeks, no difference was noted between groups in the number of patients with significant improvement in sexual function (1 of 19 participants in the bupropion group and 1 of 20 in the placebo group). Limitations were reported as potential insufficient dose of bupropion.[1]

A 2004 double-blinded RCT involving 42 patients (37 women and 5 men, 18–45 years old) compared bupropion SR 150 mg BID and placebo over 4 weeks as an antidote to SSRI-induced sexual dysfunction.[2] Patients were on stable unspecified dose of SSRIs (fluoxetine, citalopram, paroxetine, or sertraline) for 3 months; dysfunction was determined by either global or phase-specific SSRI-induced sexual dysfunction by self-report or by the Changes in Sexual Functioning Questionnaire (CSFQ). CSFQ is a 14-item questionnaire investigating 5 subscales of sexual dysfunction (pleasure, desire/frequency, desire/interest, arousal/erection, and orgasm/ejaculation) scored from 1 to 5, with higher scores indicating better function. Three patients withdrew because of adverse events associated with bupropion and 10 others because of incomplete treatment regimen and data.

Bupropion did not improve the global or desire/interest, arousal/erection, and orgasm/ejaculation subscale scores at weeks 2 or 4, but slightly improved mean desire/frequency by 1.2 points compared with 0.5 points for placebo at week 4 (maximum score of 10 points on this subscale; P=.024).[2]

A 2001 double-blind RCT randomized 30 patients (age and sex unspecified) with SSRI-induced sexual dysfunction to bupropion SR 150 mg/d or placebo for 3 weeks.[3] Patients were on SSRIs for at least 6 weeks (specific SSRIs and doses not reported). A clinically significant improvement was defined as greater than 50% improvement in ASEX score.

No patients given bupropion and 1 given placebo had a 50% improvement in overall ASEX score from baseline to week 3 (P=1.0), with no statistically significant differences between treatment groups for ASEX subcategories (sex drive, arousal, vaginal lubrication/erection, and orgasm).[3] EBP

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***EVIDENCE-BASED PRACTICE* LEARNING OBJECTIVES**

1 To become knowledgeable about evidence-based solutions to commonly encountered clinical problems.

2 To understand how ground-breaking research is changing the practice of family medicine.

3 To become conversant with balanced appraisals of drugs that are marketed to physicians and consumers.

EVIDENCE-BASED PRACTICE

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ISSN 1095-4120 (print)
ISSN 2473-3717 (online)

Vol 20 | No. 12 | December 2017 | Electronic Version

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

In pregnant women who travel, does use of compression stockings reduce risk of deep venous thrombosis (DVT)?

EVIDENCE-BASED ANSWER

Perhaps. Among nonpregnant patients with varying risks of DVT (SOR: **B**, meta-analyses of RCTs) and large cohorts that included pregnant patients (SOR: **C**, meta-analysis not limited to RCTs), treating about 29 air travelers with compression stockings prevents 1 DVT. Pregnant air travelers should take precautions to minimize risk of venous thromboembolism, including use of support stockings, periodic movement of the lower extremities, avoiding restrictive clothing, occasional ambulation, and maintenance of adequate hydration (SOR: **C**, expert opinion).

A meta-analysis of 9 RCTs (N=2,498) evaluated use of knee-length stockings (ankle pressure 14–30 mmHg) to prevent DVTs during air travel.[1] Studies included patients considered low risk (age >50 years, immobilization, and poor fluid intake), medium risk (venous insufficiency, disability limiting mobilization, and recent major pelvic surgery), and high risk (history of thromboembolism or malignancy, or a coexisting procoagulant condition). Pregnancy was not given a category or listed as a risk factor.

Use of knee length compression stockings decreased incidence of DVT compared with control (absolute difference of 3.4%; 95% CI, 2.3–4.5; number needed to treat [NNT]=29) Significant heterogeneity was noted among the studies in risk level of participants. One study included all passengers as participants, randomized into either a group that wore compression stockings or a control group that did not wear compression stockings.[1]

A systematic review of 6 case-control studies (N=3,291), 10 cohort studies (N=217,597,220), and 9 RCTs (N=3,199) evaluated risk of DVT or pulmonary embolism in air travelers, including antepartum and postpartum patients, and the efficacy of preventive measures.[2] The studies performing pre- and posttravel ultrasound found 1.2% of patients (44 of 3,820) had a DVT after air travel; however, only 2 patients were symptomatic. Pooled data from RCTs found a statistically significant decrease in incidence of DVTs with the use of graduated compression stockings (12–30 mmHg) compared with nonuse (4 trials, n=1,840; 0.2% vs 3.7%; ARR 3.5%, NNT=28; *P* value not reported).

A consensus opinion of the American College of Obstetricians and Gynecologists stated that pregnant air travelers may take precautions to ease in-flight discomfort and, although no hard evidence exists, preventive measures can be used to minimize risks of venous thrombosis, including use of support stockings, periodic movement of the lower extremities, avoiding restrictive clothing, occasional ambulation, and maintenance of adequate hydration.[3]

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Is an isolated elevation of maternal human chorionic gonadotropin (hCG) associated with adverse fetal outcomes?

EVIDENCE-BASED ANSWER

An isolated elevation in hCG is associated with an increased risk of preterm birth and fetal death (SOR: **C**, inconsistent case-control studies). Elevated hCG is not associated with increased risk of intrauterine growth restriction (IUGR), small-for-gestational-age (SGA) infants, low Apgar scores, or early preterm birth (SOR: **C**, consistent case-control studies). Among women with preeclampsia and elevated hCG, there is an increased risk of preterm birth, low birth weight, and newborn intensive care unit (NICU) admission (SOR: **C**, case-control study).

A 2003 retrospective case-control study (N=14,374) sought to determine if elevations in serum alpha-fetal protein or hCG were associated with adverse pregnancy outcomes.[1] Elevated hCG levels (>2 multiple of the mean [MoM]) were found in 9.8% of low-risk pregnancies and 9.4% of high-risk pregnancies (preexisting medical conditions, previous poor pregnancy outcome, age >36 years). Women with uncertain pregnancy dating or with eventual diagnoses of chromosomal and structural abnormalities were excluded from the study.

In all pregnancies (low and high risk), researchers found that elevations in hCG were associated with an increased risk of fetal death (relative risk [RR] 4.1; 95% CI, 2.3–7.4). The risk of preterm birth was significant only in women who were low-risk prepregnancy with medically induced preterm birth (RR 3.1; 95% CI, 1.6–7.9). No difference was noted in rates of IUGR or spontaneous preterm birth in low- and high-risk pregnancies with elevated hCG.[1]

A 2001 case-control study collected data from 485 preeclamptic primiparous women to evaluate the relationship between hCG levels and severe preeclampsia.[2] Thirty-seven women had unexplained elevations in serum hCG levels (>2.5 MoM) at 15 to 16 weeks' gestation, and 450 women had normal hCG levels. Mean age of the women (26 years) was similar between the groups. Pregnancies with known chromosomal abnormalities or multiple gestations were excluded from the study.

Researchers found that women with elevated hCG during the second trimester, compared with women who had normal hCG levels, had a significantly higher risk of preterm birth (43% vs 26%; adjusted odds ratio [aOR] 2.0; 95% CI, 1.0-4.2), low birth weight (43% vs 27%; aOR 2.1; 95% CI, 1.0–4.2), and NICU admissions (56% vs 42%; aOR 2.3; 95% CI, 1.1–4.6). No difference was noted in rates of fetal death, SGA, or low Apgar scores between pregnancies with elevated and normal hCG.[2]

A 2000 case-control study compared 3,728 pregnant women with elevated hCG levels between 14 and 18 weeks' gestation with 26,524 controls for rates low birth weight, IUGR, preterm birth, early preterm birth (<35 weeks), and fetal/neonatal death.[3] Pregnancies with known chromosomal abnormalities, neural tube defects, multiple gestation, or congenital abnormalities were excluded from the study. Control patients had otherwise healthy pregnancies without any complications listed above.

They found an increased risk of preterm birth (RR 1.1; 95% CI not given) but not early preterm birth in women with elevated hCG (>2 MoM). No significant increase was noted in relative risk of other adverse pregnancy or neonatal outcomes listed above.[3]

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What is the best treatment for erectile dysfunction in men with diabetes mellitus?

EVIDENCE-BASED ANSWER

Phosphodiesterase type 5 (PDE-5) inhibitor therapy is superior to placebo for erectile dysfunction (ED) in patients with and without diabetes. No studies directly compare PDE-5 inhibitors (SOR: **A**, systematic review and RCT). Testosterone treatment may improve sexual function in patients with diabetes and severe hypogonadism (SOR: **C**, single RCT).

A 2007 meta-analysis included 8 RCTs comparing a PDE-5 inhibitor with placebo or no treatment for relief of ED symptoms (N=1,717 male patients in heterosexual relationships, 80% with type 2 diabetes).[1] Treatment with sildenafil (25, 50, 100 mg), vardenafil (10, 20 mg), tadalafil (10, 20 mg), or control lasted for an average of 12 weeks. The primary outcome in all studies was global efficacy using the question, "Did the treatment improve your erection?"

All studies showed significant improvement in ED with PDE-5 treatment compared with placebo (relative risk [RR] for a "yes" answer 3.8; 95% CI, 3.1–4.5).[1]

An additional primary outcome of the same study measured the International Index of Erectile Function (IIEF, a validated 5-item questionnaire scored 1–5 for each component: confidence in erection, erection difficulty, successful penetration, erection duration, and overall sexual satisfaction, in which low scores are associated with worse outcomes). The use of PDE-5 inhibitors significantly improved IIEF scores (weighted mean difference 6.6; 95% CI, 5.2–7.9). No RCT in the meta-analysis directly compared PDE-5 inhibitors, and no RCT compared PDE-5 inhibitors with other treatment options for ED. Findings were limited by significant heterogeneity in ages of patients and treatment regimens.[1]

A 2016 RCT compared testosterone undecanoate 1,000 mg intramuscular [IM] with placebo in patients 18 to 80 years old with diabetes and hypogonadism identified by screening at primary care clinics (N=199).[2] Testosterone deficiency was characterized as mild (total testosterone 8.1–12 nmol/L or free testosterone 0.18–0.25 nmol/L) or severe (total testosterone ≤8 nmol/L or free testosterone ≤0.18 nmol/L). Patients received testosterone IM or placebo at weeks 0, 6, and 18.

At 30 weeks, patients with severe deficiency treated with testosterone had a significantly higher mean IIEF score than patients given placebo (5.8-point difference between groups; *P*=.0036). No significant difference was noted in IIEF score for treated patients with mild deficiency. At 30 weeks, adverse events in the severe deficiency group treated with testosterone included an increase in mean hematocrit (from 43.5% to 45.6%; *P*=.013) and an increase in mean prostate-specific angtigen (from 1.2 to 1.5 µg/L; *P*=.002).[2]

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For women with low-risk pregnancies, does air travel increase rates of pregnancy complications?

EVIDENCE-BASED ANSWER

The answer is unclear. Data are conflicting on airline travel with cabin pressure comparable to more than 1,500 m and its relationship with pregnancy duration (No SOR given). No effect was found on low birth weight (SOR: **C**, retrospective cohort study).

A 2004 retrospective cohort study evaluated 222 women carrying a singleton nonanomalous fetus who were admitted for delivery at a single center.[1] Overall, 37% were nulliparous. Participants were questioned as to the frequency and duration of airline travel during pregnancy (typical passenger airline cabin pressure is similar to elevations of 1,800–2,400 m).

The authors compared pregnant women who reported a history of airline travel with pregnant women who had not, and found no difference in gestational age at delivery (39.1 vs 38.4 weeks; *P*=.07); neonatal low birth weight (3,379 vs 3,273 g; *P*=.24), or a cumulative adverse obstetric outcome, which included stillbirth, 5-minute Apgar score, delivery at

less than 37 weeks, or birthweight less than 10th percentile (odds ratio [OR] 0.67; 95% CI, 0.33–1.3).[1]

A 2006 retrospective cohort study, modeled after the 2004 study but including different outcome measures, evaluated 992 women carrying a singleton, nonanomalous fetus who were admitted for delivery at a single center.[2] Overall, 56% were primigravid. The authors excluded women who received tocolysis for preterm labor. Women were questioned as to the frequency and duration of airline travel during their pregnancy and were compared with pregnant women who had not traveled.

A statistically significant increase was found in late preterm delivery (34–37 weeks) (adjusted odds ratio [aOR] 2.2; 95% CI, 1.1–4.5) among women who had travelled by air. Subgroup analysis revealed this increase was statistically significant in primigravid women (aOR 1.5; 95% CI, 1.2–1.8) but not multigravid women (aOR 1.0; 95% CI, 0.58–2.2). The average flight length for primigravid women was 7.8 hours, compared with 5.6 hours for multigravid women ($P<.01$).[2]

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What is the relationship between anorexia nervosa and miscarriage?

EVIDENCE-BASED ANSWER

Although miscarriage may be associated with binge eating disorder and atypical bulimia nervosa, no association is apparent between anorexia nervosa and miscarriage (SOR: **B**, retrospective case-control study and cohort study).

A 2013 retrospective case-control study (N=2,257) compared adverse perinatal outcomes in pregnant patients with eating disorders treated at a Helsinki hospital from 1995 to 2010 with those of matched controls from the Helsinki Central Population Register.[1] Applying criteria of the International Statistical Classification of Diseases and Related Health Problems 10th revision retrospectively, 502 patients were diagnosed with anorexia nervosa, 365 with atypical anorexia nervosa, 786 with bulimia nervosa, 445 with atypical bulimia nervosa, and 149 with binge eating disorder. A classification of *atypical* anorexia or bulimia implies that the eating disorder has features that closely resemble the typical eating disorder but does not meet all of the specific diagnostic criteria.

No difference was noted in miscarriage rate in patients diagnosed with anorexia nervosa when compared with controls (23% vs 18%; odds ratio [OR] 1.4; 95% CI, 0.96–2.2) or in patients with atypical anorexia nervosa when compared with controls (22% vs 18%; OR 1.4; 95% CI, 0.95–2.1). However, patients with a diagnosis of atypical bulimia had a higher incidence of miscarriage than controls (21% vs 18%; OR 1.4; 95% CI, 1.0–2.0) but patients with bulimia nervosa did not. The largest difference in occurrence of miscarriage was seen in the binge eating disorder group compared with controls (47% vs 23%; OR 3.3; 95% CI, 1.5–6.7). Because the study population was taken from an eating disorders clinic, generalizing the results to a less focused population is difficult. The study did not report comorbidities, the potential for confounding diagnoses, nor did the study discuss the temporal relationship between the eating disorder disease course and associated miscarriages.[1]

A 2007 longitudinal cohort study (N=11,700) reviewed the characteristics and outcomes of pregnancies first identified in Avon, England in 1991 to 1992 and compared the rates of miscarriage and major adverse perinatal outcomes of the general population to those of women with a diagnosis of eating disorder.[2] Out of 11,700 women, 159 (1.4%) self-reported anorexia nervosa via a questionnaire. Adjustments were made to account for maternal age, parity, lifetime alcohol use, and lifetime smoking.

The rate of miscarriages in the women with anorexia nervosa was similar to that of the general population (OR 1.0; 95% CI, 0.7–1.6). Weaknesses of the study included using a diagnosis of anorexia nervosa through self-reporting and the inability to establish the temporal course of the miscarriages and anorexia symptoms.[2]

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Is a brief intervention effective in managing and decreasing severe alcohol use?

EVIDENCE-BASED ANSWER

Yes. Brief interventions decreased alcohol consumption by 19 to 51 g per week for at least a year in nondependent adults with excessive alcohol consumption (SOR: **C**, meta-analyses of RCTs of disease-oriented evidence).

A 2007 systematic review evaluated the effect of brief interventions to reduce alcohol consumption in excessive drinkers.[1] The review included 22 RCTs with 7,619 patients (5,860 after dropouts) in the primary meta-analysis, measuring change in alcohol consumption after brief interventions. Participants were 70% male in an outpatient primary care setting with a baseline alcohol consumption ranging from 89 to 456 g/wk (mean 313 g/wk). The brief interventions were mostly between 1 and 4 sessions, generally limited to 5 to 15 minutes each, and provided advice and information aimed at reducing risky alcohol consumption or alcohol-related problems.

Brief interventions reduced alcohol consumption at 1 year by an average of 38 g (95% CI, 23–54) per week compared with controls, which included assessment only, standard treatment, or nonintervention. In subgroup analysis by sex, men reduced consumption by an average of 57 g (8 trials, n=1,808; 95% CI, 25–89), but women did not significantly reduce consumption (5 trials, n=499; mean difference [MD] –10 g; 95% CI, –48 to 29). However, the difference between men and women was not statistically significant.[1]

A 2015 systematic review involving 6 meta-analyses and 1 systematic review of RCTs (with 7–22 trials, 2,716–7,619 patients) studied the effectiveness of brief interventions in a primary healthcare setting to decrease alcohol consumption.[2] The systematic review above was included in this systematic review and had the largest sample of participants. Patients were 17 to 70 years old and predominantly nondependent drinkers labeled as hazardous, at-risk, or excessive drinkers because of alcohol consumption above the recommended limits.

Five meta-analyses (N not given) reported change in consumption and showed brief interventions between 5 and 15 minutes over multiple sessions resulted in a moderate decrease of alcohol consumption (19–51 g/wk) at the end of the study periods (typically 1 year) versus controls (controls varied by study). Results were reported to be maintained at 6-months follow-up. Interventions longer than 15 minutes did not improve outcomes compared with shorter interventions. Four reviews reported subgroup analysis based on sex and found conflicting results regarding effectiveness in men and women.[2]

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Does vitamin D supplementation offer any benefit in patients with depression?

EVIDENCE-BASED ANSWER

No. Evidence does not support the use of vitamin D supplementation as a therapy for depressive symptoms in patients with a clinical diagnosis of depression (SOR: **A**, meta-analyses and RCTs).

A 2015 meta-analysis consisted of 9 RCTs with 4,923 patients who had a diagnosis of major depressive disorder.[1] The studies evaluated the role of variable doses of supplemental vitamin D or placebo to reduce depressive symptoms. Vitamin D doses varied from 400 IU daily to 2 million IU BID. The mean age of patients in the studies ranged from 22 to 75 years (overall median 47 years). The study duration varied; 1 study was only 5 days and the remainder ranged from 6 weeks to 5 years. In each of the studies, depressive symptoms were measured pre- and postintervention using validated assessment scales such as the Beck's Depression Inventory and Geriatric Depression Scale.

No statistically significant reduction was noted in depressive symptoms for patients receiving vitamin D

supplementation compared with placebo (9 trials, n=4,923; standard mean difference 0.28; 95% CI, –0.14 to 0.69).[1]

A 2016 randomized, double-blind placebo-controlled trial evaluated the role of vitamin D supplementation on depressive symptoms and markers of oxidative stress.[2] The study included 40 patients (34 women and 6 men) between 18 and 65 years old with a diagnosis of major depressive disorder based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, and a Hamilton Depression rating of 15 or more. Participants could not have cardiovascular, liver, or renal disease, be pregnant, or have baseline vitamin D supplement use. Beck Depression Inventory scores were measured before and after 8 weeks of supplementation with 50,000 IU of vitamin D.

No difference was noted in depressive symptoms between vitamin D and placebo groups at 8 weeks (reduction of Beck score of –8 vs –3.3 points; *P*=.06).[2]

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Do antibiotics improve outcomes in the management of acute uncomplicated diverticulitis?

EVIDENCE-BASED ANSWER

No, antibiotics do not appear to reduce the complication rate, length of hospital stay, or recurrences in the treatment of acute uncomplicated diverticulitis (without abscess, fistula, free air, peritonitis, sepsis, or immune suppression). Complication rates in uncomplicated diverticulitis are 1% to 3% with or without antibiotics (SOR: **B**, single high-quality RCT and 2 observational studies conducted by 1 research group).

A 2012 review of the effects of antibiotics in uncomplicated diverticulitis[1] included 1 multicenter RCT of 623 adults (>18 years old) with computed tomography (CT)-verified acute uncomplicated diverticulitis randomized to antibiotics or placebo.[2] Uncomplicated diverticulitis was defined as no abscess, fistula, or free air on imaging, nonpregnant, no immunosuppressive therapy, and no signs of peritonitis or sepsis.

The intervention group first received either a combination of a second- or third-generation cephalosporin and metronidazole, or a carbapenem, or piperacillin-tazobactam parenterally and then transitioned to oral ciprofloxacin or cefadroxil combined with metronidazole (timing and criteria for oral antibiotics not stated) for a total duration of at least 7 days. Measured outcomes included complication rates (abscess formation or perforation), length of hospital stay, and recurrence of symptoms within a year.[1]

Complication rates were similar in the antibiotic and control groups (1% vs 1.9%; *P*=.3). Length of hospital stay (3 days) and recurrence of diverticulitis at 12-month follow-up (16%) were also similar in both groups.[1]

A prospective case series from the same research group investigated the safety of outpatient management of CT-verified acute uncomplicated diverticulitis without antibiotics in 155 adults.[3] Patients received counseling on bowel rest and paracetamol for pain. Progress was monitored by patient-recorded daily pain score, daily phone calls with a registered nurse, then a follow-up office visit in 1 week and again at 3 months with a surgeon. Examined outcomes included resolution of symptoms without antibiotics and complication rates (perforation or abscess formation).

Of the 155 recruited patients, 4 patients (2.6%) had "treatment failure" requiring antibiotics within 1 month. Two of these patients had perforation; 1 patient had a normal CT scan but worsening symptoms; and the fourth patient had an abscess identified on CT. All 4 of these patients were managed with antibiotics alone and did not require surgery. Five patients (3.3%) had recurrence of diverticulitis within 3 months, and 16 patients (10.3%) had recurrence within 1 year.[3]

A retrospective cohort study from the same research group evaluated 195 patients (mean age 60 years) with uncomplicated CT-verified diverticulitis (defined as above) after a change in local guidelines recommending against antibiotic use for uncomplicated diverticulitis; 178 patients were treated without antibiotics and 17 received antibiotics (type of antibiotic not specified).[4] Reasons cited for antibiotic administration included pneumonia,

endometriosis, prophylaxis for laparoscopy, rising C-reactive protein, suspected appendicitis, or prescribed by an outside physician. Examined outcomes included abscess formation rates, recurrence rates, and readmission rates.

In the nontreatment group, only 6 (3.4%) were readmitted, of which 2 developed abscesses. The no-antibiotic group compared with the antibiotic group had a shorter hospital stay (1.9 vs 5.4 days; *P*<.001) and a lower recurrence rate at 12 months (13% vs 24%; *P*=.019).[4]

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Do patients taking combined oral contraceptives experience mood changes compared to patients not taking combined oral contraceptives?

EVIDENCE-BASED ANSWER

Yes. Most patients taking combined oral contraceptives (COCs) experience mood changes. Many experience improved mood, decreased depressive symptoms, and decreased anxiety; fewer patients will experience increased anxiousness and depressive symptoms (SOR: **B**, systematic reviews not limited to RCTs, and an RCT).

A 2012 systematic review of 26 RCTs, open-label observational trials, prospective cohort studies, and population-based cross-sectional studies involving more than 35,000 women evaluated mood changes in women taking oral contraceptives.[1] Most patients taking COCs experienced mood changes and most of the changes were positive.

For instance, 1 prospective cohort study reported on 3,679 women without prior COCs use who were treated with ethinyl estradiol (EE) 20 µg and desogestrel for 3 months. Of those, 62% reported reduced nervousness and 71% reported fewer depressive symptoms on the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Overall, 10% reported worsening of depressive mood, and 6.7% increased nervousness. The retrospective studies reported higher levels of negative side effects. For example, a retrospective observational study reported that of 1,466 women using COCs, 13% reported being more irritable, 1.3% reported increased anxiety, and 10.3% reported feeling more depressed (compared with 8.8% who reported less irritability, 13% who reported less anxiety, and 5.7% who reported less depressed mood).[1]

A separate 2012 systematic review of 24 studies (7 included in the above systematic review) including prospective cohort, observational, longitudinal, population studies, and case reports involving more than 125,000 participants studied the effect of various forms of contraception, including COC, levonorgestrel implant, and depot medroxyprogesterone, on clinical depression.[2] This study differed from the previous systematic review in that the authors reviewed only controlled trials that used validated depression scales to determine the effect of various hormonal contraceptives compared with placebo on patients diagnosed with clinical depression.

Of the 21 COC studies, 3 studies (total n=52,096) found improved mood symptoms, 10 studies (n=26,052) found no significant difference, and 8 studies (n=46,629) found worsened depression. No attempt was made to synthesize the data, as not enough studies used validated depression screening tools.[2]

A subsequent RCT (N=34) again investigated the effect of COCs on mood.[3] Healthy women (18–45 years old) with regular periods, a reported history of depressed mood, decreased interest in usual activities, anxiety, mood swings, or irritability during previous COC use were randomized to receive EE 30 mg with 0.15 mg levonorgestrel or placebo. The exclusion criteria included a family history of venous thrombosis, previous neurological diagnoses, current psychiatric disorder, and use of the following medications within 2 months of study inclusion: hormonal contraceptives, cortisol, levothyroxine, or psychotropic drugs.

The women were given daily surveys using the Cyclicity Diagnoser, a 9-question Likert-scale survey in which the participants rated physical and emotional symptoms from 0 (no symptoms) to 8 (maximum possible symptoms). The

survey was administered daily during the pretreatment period that lasted 1 full menstrual cycle and daily for the 21-day study period.[3]

One-third of the study participants in the treatment group experienced mood changes. Although most participants experienced no negative mood effects, a statistically significant increase was noted in depressed mood (Student's t-score=–2.3, $P<.05$), mood swings (t score=–3.4, $P<.01$), and fatigue (t score=–3.1, $P<.01$) during the third week of the study phase compared with the placebo group. Weaknesses included small study size, short duration, and lack of generalizability (history of prior adverse effects, broad exclusion criteria).[3]

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In overweight or obese adults, does increased daily fiber intake result in more weight reduction compared to routine fiber intake?

EVIDENCE-BASED ANSWER

Probably not. A bean-based high fiber is not superior to a low-carbohydrate diet for weight loss (SOR: **C**, conflicting RCTs). Fiber goals may be easier to reach with a bean-based diet than a fruit, vegetable, and grain-based diet (SOR: **C**, small RCT).

A 2013 RCT of 173 obese men and women with a body mass index (BMI) of 30 to 44 kg/m^2 compared a high-fiber diet rich in beans (>40 g fiber daily for women and >50 g fiber daily for men) with a low-carbohydrate diet (<120 g daily, fiber intake 20–25 g) over 16 weeks.[1] Participants were provided education on the diet during a 3-week preparation phase and completed a 1-week dietary induction phase where they consumed 7 prepared meals showcasing their assigned diet. During dietary maintenance phase visits at 6, 8, 12, 14, and 16 weeks, patients received meal plans and recipes with a dietary support telephone call at week 10.

At 16 weeks, both groups demonstrated weight loss (mean of 4.1 kg in the high-fiber group and 5.2 kg in the low-carbohydrate group; $P=.2$). The high-fiber group reported more events of gas (9 vs 1) and cramps (6 vs 0) than the low-carbohydrate group but less constipation (2 vs 4) and fatigue (2 vs 3); however, statistical analysis not reported. The study was limited by high dropout rate (29% at 16 weeks) and fewer men than women.[1]

A 2013 double-blind RCT compared the intake of a soy fiber biscuit (27.5 g fiber, 309 Kcal) with a low-fiber biscuit (3.2 g fiber, 375 Kcal) on body weight in 39 healthy college-age adults with a BMI of 23 to 35 kg/m^2 over 12 weeks.[2] Baseline characteristics between the 2 groups were similar including dietary fiber intake. Patients were otherwise instructed to maintain current diet and exercise routines.

After 12 weeks, the soy fiber group lost more weight than the low fiber biscuit group, although the absolute change in both groups was small (1.4 vs 0.68 kg; $P=.045$).[2]

A 2013 pilot RCT explored the effects on weight of a high-fiber bean-based diet (1.5 cups dried beans per day) versus a high-fiber diet based on fruits, vegetables, and grains in 2 men and 17 women aged 18 to 70 years with BMI of 27 to 35 kg/m^2 over 4 weeks.[3] Both groups were given a 1,400 kcal/d diet with a goal fiber intake of 25 g and were asked to keep a food log for 3 days each week. The bean group averaged 29.1 g/d of fiber and met the dietary fiber intake goal 3.1 out of the 4 weeks. The fruits, vegetable, and grains group averaged 28.9 g/d of fiber and met the fiber goal 2.3 out of 4 weeks.

After 4 weeks, the bean group lost more weight than the fruits, vegetables, and grains group, although the magnitude of weight loss in both groups was small (1.6 vs 1.1 kg; $P<.0001$).[3]

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What is the best treatment for recurrent methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections?

EVIDENCE-BASED ANSWER

For patients with colonized methicillin-resistant *S aureus* (MRSA), chlorhexidine wash, nasal mupirocin, oral rifampin, and oral doxycycline doubles decolonization rates compared with no treatment (SOR: **B**, small RCT), while a similar regimen of nasal mupirocin, hexachlorophene wash, and oral antibiotics is associated with a marked reduction in the recurrence rate of MRSA infections (SOR: **C**, small prospective cohort). Mupirocin plus chlorhexidine is no better than chlorhexidine alone for decolonization (SOR: **B**, small RCT). Recurrent infections may be treated with decolonization therapy with mupirocin with or without topical antiseptic solution or dilute bleach baths (SOR: **C**, expert opinion).

A 2007 Canadian RCT evaluated MRSA eradication from colonized adults (N=112) after a 7-day decolonization regimen.[1] The treatment group (n=87) received 2% chlorhexidine daily wash, 2% mupirocin ointment to nares 3 times daily, oral rifampin 300 mg twice daily, plus doxycycline 100 mg twice daily. The comparison group (n=25) received no treatment. Colonization was determined if any cultured site was positive.

At the 3-month follow-up, treatment resulted in eradication of MRSA colonization in 74% of patients compared with 32% in the no-treatment group, although the reported relative risk (RR) does not match the reported eradication rates (RR 1.6; 95% CI, 1.2–2.0; number needed to treat=3).[1]

A 2012 prospective cohort followed 31 patients (18–80 years old) with more than 2 MRSA skin infections in the prior 6 months and no active infection to evaluate a 3-step decolonization regimen for reducing skin infection recurrence over 6 months.[2] The regimen included 2% mupirocin ointment to nares twice daily, 3% hexachlorophene body wash daily, and an oral antibiotic (trimethoprim-sulfamethoxazole, minocycline, or doxycycline at the investigators' discretion, dosing regimens not reported) administered concomitantly for 10 days.

Treatment reduced mean infection rate compared with pretreatment infection rate (0.03 infections/month after treatment vs 0.84 infections/month prior; $P<.0001$).[2]

A 1999 Swedish double-blind RCT compared MRSA carriage rates (defined as ≥1 positive MRSA cultures from any body site) after treatment with 2% mupirocin ointment applied to nares twice daily (n=48) for 5 days with placebo (n=50) in adults older than age 16.[3] Both groups performed daily chlorhexidine (unknown concentration) body washes during the 5-day intervention. Follow-up with cultures from nares, groin, pressure sores, lacerated skin sites, and urine occurred on days 12, 19, and 26 after therapy initiation.

No difference was noted in mupirocin and chlorhexidine vs placebo and chlorhexidine for recurrence of MRSA colonization (25% in treatment group vs 18% in control group; $P=.40$).[3]

The 2011 clinical practice guidelines on treatment of MRSA infection by the Infectious Diseases Society of America recommended education regarding keeping wounds covered and clean, maintaining good personal hygiene, and avoiding reusing or sharing personal items to prevent recurrent MRSA skin and soft tissue infections (A-III, good evidence to support from opinion and experience).[4] Decolonization was recommended for recurrent skin and soft tissue infections or recurrent household transmission using mupirocin twice daily for 5 to 10 days with or without a skin antiseptic solution such as chlorhexidine daily for 5 to 14 days or dilute bleach baths for 15 minutes twice weekly for 3 months (C-III, poor evidence to support from opinion and experience). Oral antibiotics were not routinely recommended.

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Does glucosamine and chondroitin in combination increase function in patients with osteoarthritis of the knee?

EVIDENCED-BASED ANSWER

The combination of glucosamine and chondroitin over 1 to 2 years does not significantly increase function in patients with knee osteoarthritis (OA) (SOR: **A**, multiple RCTs). However, the combination may improve function in patients with moderate to severe OA at 24 weeks (SOR: **B**, single RCT).

In a 2015 RCT (N=605), glucosamine, chondroitin, and the combination were evaluated in patients with knee OA.[1] The mean age of participants was 60 years, just over 50% were women, and approximately half of the study population had mild radiographic OA (Kellgren and Lawrence grade <2) whereas the other half had moderate to severe OA (grade 2–4).

Primary outcomes were medial tibiofemoral joint space narrowing and knee pain; secondary outcomes included the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) physical function scores. The 17 questions in the physical function subscale include difficulty in rising from a seated position and putting on socks (Likert format rated 0–4 for total score of 0–68, with higher scores indicating a greater loss of function). Patients received glucosamine sulfate 1,500 mg daily, chondroitin 800 mg daily, both glucosamine sulfate and chondroitin (doses unchanged), or placebo.[1]

Combined treatment did not improve function any more than placebo at 1 or 2 years. WOMAC scores at 2 years were 17.8 in both groups (*P*=.99).[1]

In a 2006 RCT (N=1,583), glucosamine and chondroitin sulfate were evaluated in patients with knee OA over 24 weeks.[2] The mean age of the patients was 59 years, and 64% were women. Participants were stratified according to the severity of knee pain (mild, moderate, severe) using the WOMAC pain score. Patients had clinical and radiographic evidence (Kellgren and Lawrence grade 2 or 3) of OA. Assigned treatment groups included glucosamine 500 mg 3 times daily, chondroitin sulfate 400 mg 3 times daily, both glucosamine and chondroitin sulfate (doses unchanged), celecoxib 200 mg daily, or placebo.

The primary outcome was a 20% reduction in pain; response in WOMAC function score was one of the secondary outcomes (this study used a 0–100 scale for each of the 17 questions, total score 0–1,700, higher scores indicating greater loss of physical function). Over 24 weeks, combined treatment in patients with moderate-to-severe pain (n=72) decreased WOMAC function score by 474 points compared with a decrease of 292 points with placebo (*P*=.008). However, combined treatment in patients with mild pain (n=245) did not decrease WOMAC function score more than placebo (221 vs 209 points (*P*=.71) and neither did combined treatment in the entire group.[2]

In the 2010 extension of the above study (N=662), glucosamine and chondroitin sulfate were evaluated in patients with OA-related knee pain over 2 years.[3] The randomized study groups and dosages were unchanged from the above study. The primary outcome was the odds of reaching a 20% reduction in WOMAC pain score over 24 months. A response in WOMAC function was one of the secondary outcomes (scaled to a 0–100 score).

At 2 years, combined glucosamine and chondroitin sulfate therapy did not significantly improve function score compared with placebo (20 vs 23 points, mean difference 3.2; 95% CI, –2.2 to 8.6). Subgroup analysis based on severity of OA was not performed.[3]

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What are effective treatments for temporomandibular joint (TMJ) syndrome?

EVIDENCE-BASED ANSWER

Gabapentin may reduce TMJ pain by about 30% over placebo, while NSAIDs have demonstrated inconsistent effects (SOR: **C**, low-quality RCTs). Corticosteroid and sodium hyaluronate injections have similar short-term short outcomes (although the effect versus placebo is unknown), but sodium hyaluronate may be better at 6 months (SOR: **C**, systematic review with conflicting low-quality RCTs).

A 2010 systematic review and meta-analysis identified 11 RCTs (N=496) that compared different pharmacologic interventions for relief of pain in TMJ disorder. This review included RCTs of adults who met TMJ diagnostic criteria and were given oral agents.[1]

One 1996 RCT (n=32) that compared diclofenac (50 mg 3 times a day) with placebo in patients with TMJ demonstrated no significant difference in daily pain at 2-week follow-up (relative risk 0.71; 95% CI, 0.49–1.04). Another RCT (n=68) found naproxen (500 mg twice daily for 6 weeks) was superior to placebo at reducing TMJ pain on an 11-point visual analog scale (VAS) (mean difference [MD] –1.7; 95% CI, –2.1 to –1.3). In a 12-week RCT (n=44), gabapentin was found to be superior to placebo at reducing TMJ pain on an 11-point VAS (MD –3.2; 95% CI, –4.7 to –1.7). Benzodiazepines, topical capsaicin, glucosamine, COX-2 inhibitors, muscle relaxers, and propranolol did not significantly reduce pain in patients with TMJ. Due to risk of bias in the positive studies, the authors concluded that evidence was insufficient to support the effectiveness of any pharmacologic agents at reducing pain for TMJ.[1]

A 2013 systematic review of 9 RCTs (N=472) reviewed the effectiveness of short-term (4-week follow-up) and long-term (3- to 6-month follow-up) intraarticular injections with corticosteroids and sodium hyaluronate on pain relief in patients with TMJ.[2] The steroids used included methylprednisolone and betamethasone (doses not provided). For this study, no placebo was used for comparison. Meta-analysis was not performed.

Intraarticular corticosteroid and sodium hyaluronate injections were reported to be equally effective at reducing pain in all 3 of the short-term trials (n=124). For long-term outcomes, 2 trials (n=159) showed sodium hyaluronate injections were more effective in reducing pain than saline injections and 1 trial (n=40) showed sodium hyaluronate was more effective than corticosteroid injections in reducing pain, while another trial (n=36) showed no difference between the 2 agents. The review was limited by small study sizes, lack of reporting of injection protocols, magnitude of differences between the treatments, and the lack of use of a placebo.[2]

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What nonnarcotic oral analgesics are the safe for patients taking warfarin?

EVIDENCE-BASED ANSWER

The answer is not entirely clear. COX-2 inhibitors appear safer than nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) for patients taking warfarin (SOR: **B**, cohort and case-control studies). Acetaminophen increases the international normalized ratio (INR) in patients taking warfarin by 0.67 to 0.83 over placebo, but with unclear clinical effect (SOR: **C**, small RCTs with disease-oriented outcomes).

A 2009 retrospective cohort study over a 5-year period examined the rates of hospital admission for gastrointestinal (GI) bleeding of any severity in patients (mean age 67 years) taking warfarin plus a nonselective NSAID such as ibuprofen, naproxen, etodolac, nabumetone, or indomethacin (n=8,169); warfarin plus a selective COX-2 inhibitor such as celecoxib or rofecoxib (n=1,601); or warfarin alone (n=36,444).[1] Eligible patients had received a new prescription for warfarin after

the study period started and before it ended, and were excluded if taking warfarin during the 6 months before the index date.

Compared with warfarin use alone, the adjusted hazard ratio (aHR) for hospitalization for GI bleeding with nonselective NSAID use was 3.6 (95% CI, 2.3–5.5) and with COX-2 selective use was not significant at 1.7 (95% CI, 0.6–4.8). Risk of admission for GI bleeding was higher with nonselective NSAIDs plus warfarin than with COX-2 inhibitors plus warfarin (aHR 3.7; 95% CI, 1.4–9.6).[1]

A 2005 retrospective cohort study over a 40-month period reviewed bleeding complications in patients taking warfarin plus the selective COX-2 inhibitor celecoxib (100 or 200 mg, once or twice daily; 123 patients, average age 59 years), compared with patients taking warfarin alone (1,022 patients, average age 61 years).[2] Bleeding complications were defined as either major (resulting in hospitalization, blood transfusion, or death) or minor. No difference was noted in minor bleeding complications (relative risk [RR] 1.3; 95% CI, 0.7–2.6) or major bleeding complications (RR 1.0; 95% CI, 0.14–7.6).

A 2005 case-control analysis evaluated 361 elderly patients taking warfarin admitted for GI hemorrhage over a 1-year period compared with 1,437 age- and sex-matched control patients taking warfarin but without admission for GI hemorrhage.[3] Case patients were more likely to have been prescribed a nonselective NSAID (odds ratio [OR] 1.9; 95% CI, 1.4–3.7) or celecoxib (OR 1.7; 95% CI, 1.2–3.6) in the 90 days before admission than matched control patients.

A 2011 RCT of 45 adult patients (21–83 years old) compared the effect of acetaminophen (2 or 3 g/d for 10 days) on INR with placebo.[4] Patients were taking stable warfarin therapy, defined as taking 2 to 9 mg for more than 30 days with 2 consecutive INR values within target range on the same dose of warfarin within 2 weeks of study enrollment. Participants were excluded if they were taking medication known to interact with oral anticoagulant therapy or acetaminophen within the prior 14 days.

Compared with placebo, acetaminophen increased the mean maximal INR by 0.70 (P=.01) and 0.67 (P=.01) at 2 and 3 g/d, respectively. No bleeding events were observed, but the study was likely underpowered to detect a difference.[4]

A 2006 randomized, double-blind, placebo-controlled trial of 20 outpatients (aged 24–89 years) taking stable warfarin therapy (2–9 mg for >30 days) compared the effect of acetaminophen (4 g/d for 14 days) on INR versus placebo.[5] Patients were included if taking potentially interacting medications with warfarin as long as the warfarin dose remained the same.

The maximum mean increase of INR in patients taking acetaminophen was 1.2 versus 0.37 in the placebo group (P<.001). No bleeding events were observed in either group, but the study was likely underpowered for this outcome.[5]

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In patients with impingement syndrome of the shoulder, is physical therapy superior to subacromial corticosteroid injection?

EVIDENCE-BASED ANSWER

Physical therapy (PT) and corticosteroid injections are likely equivalent in decreasing pain and improving function in patients with impingement syndrome at 6 months although corticosteroids may be more effective in the first few months (SOR: **B**, systematic review of low-quality RCTs). Exercise therapy is generally recommended first, but steroid injection may be considered for severe symptoms in the first 8 weeks (SOR: **C**, expert opinion).

A 2016 systematic review of 60 RCTs (N=3,620) assessing PT for treatment of rotator cuff disease included a subcategory of 5 RCTs (n=507) comparing PT with corticosteroid injections.[1] Patients were adults (>16 years old) with subacromial impingement syndrome, rotator cuff

tendonitis/tendinopathy, subacromial bursitis, or rotator cuff tears. PT interventions varied in frequency (6–10 sessions) and duration (3–18 weeks), and included different combinations of manual therapy, range-of-motion, therapeutic ultrasound, and exercise programs. Corticosteroids varied from a single injection to 3 injections over varying lengths of time. Because of heterogeneity in diagnoses, outcome measures, and follow-up periods, meta-analysis was not feasible.

One RCT (n=82) found corticosteroid injection slightly superior to PT at 11 weeks in mean pain scores (9.2 vs 11.5 on a 28-point pain scale; mean difference 2.3; 95% CI, 0.50–4.1); however, this difference was likely not clinically significant. Three other RCTs showed no significant difference in pain over 4 to 12 months. No significant differences were seen in function on various scales (5 trials), quality-of-life scores (2 trials), or nighttime pain (1 trial). Global treatment success (not defined) was seen more frequently with corticosteroid injection at 6 weeks (1 trial, n=198; risk ratio [RR] 0.33; 95% CI, 0.14–0.79) and 11 weeks (1 trial, n=82; RR 0.58; 95% CI, 0.41–0.81), but no difference was noted at 6 months (1 trial, n=196). One trial also looked at adverse effects; none were noted with exception of transient pain related to injection. Studies were limited by lack of blinding.[1]

The University of New South Wales in Australia recently released practice guidelines on management of rotator cuff syndrome.[2] Evidence was derived from a search of multiple databases and included published clinical guidelines, systematic reviews, and research studies.

Corticosteroid injections were recommended for people "… with persistent pain or who fail to progress following initiation of an active, non-surgical treatment program…" (Grade A, based on systematic review[s] or several RCTs). PT was recommended as 1 component of an active, nonsurgical treatment (Grade B, based on 1–2 RCTs or several observational studies).[2]

In 2014, the Dutch Orthopaedic Association released a guideline on subacromial pain syndrome based on a literature search of international guidelines, systematic reviews, and scientific studies.[3] Corticosteroid injections were determined to be more effective than placebo or PT in the first 8 weeks of symptoms, but in the long term (periods >3 months) the comparison was unclear (Level 1, based on 2 high-quality RCTs). Exercise therapy was recommended to improve pain and function, especially exercises focused on the rotator cuff and scapular stabilizers (Level 1–2, based on 1–2 high- to moderate-quality studies). Per the guideline, after 1 to 2 weeks of relative rest, exercises can be started, then corticosteroid injections may be used for severe pain during the first 8 weeks.

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What is the efficacy of medication versus CBT or both for the treatment of depression in adolescents?

EVIDENCE-BASED ANSWER

At 3 months, fluoxetine alone is about as effective as the combination of fluoxetine and cognitive behavioral therapy (CBT) and either is more efficacious than CBT alone. However, by 9 months, these differences disappear and all 3 treatments appear equivalent (SOR: **B**, RCT with follow-up study).

The 2004 multicenter RCT evaluated CBT and fluoxetine in 439 adolescent patients, aged 12 to 17 years old, with a diagnosis of major depression disorder.[1] Patients were not currently taking an selective serotonin reuptake inhibitor and had a Child's Depression Rating Scale Revised (CDRS-R) score of 45 or more at baseline, indicating at least moderate depressive symptoms. Patients were randomized into 4 treatment groups and were followed for 12 weeks.

The groups were (1) fluoxetine alone (10–40 mg/d); (2) CBT alone, in which CBT was a skills-oriented treatment of 15 sessions, 50 to 60 minutes per session, over 12 weeks; (3) CBT plus fluoxetine (10–40 mg/d); or (4) placebo. The fluoxetine- and placebo-alone groups were double-blinded, while CBT alone and CBT plus fluoxetine were not blinded. Outcomes were measured at 6 and 12 weeks using the

Clinical Global Impressions (CGI) improvement scale, which rates degree of improvement in depression symptoms on a 1-to-7 scale. A score of 1 indicates very much improved and 2 indicates much improved.[1]

After 12 weeks, response rates, defined as a CGI score of 1 or 2, were 71% (95% CI, 62–80) for CBT plus fluoxetine; 61% (95% CI, 51–70) for fluoxetine alone; 43% (95% CI, 34–52) for CBT alone; and 35% (95% CI, 25–44) for placebo. Between-group comparisons of response rates indicated the combination of CBT plus fluoxetine did not differ from fluoxetine alone (*P*=.11), but was better than CBT alone (*P*=.001) and placebo (*P*=.001). Additionally, fluoxetine alone was superior to CBT alone (*P*=.01) and placebo (*P*=.001). CBT was not different from placebo.[1]

A 2007 follow-up RCT of the trial above (N=270 adolescents), evaluated outcomes at 36 weeks.[2] Nonresponders and the placebo group were removed from the study, and some children chose not to continue. All treatment was open label after 12 weeks.

At 12 weeks, response rates (again defined as a CGI improvement score of 1 or 2) among patients who elected to continue were 73% for combination therapy, 62% for fluoxetine therapy (*P*=.12 vs combination), and 48% for CBT (*P*<.001 vs combination). At 18 weeks, response rates were 85% for combination therapy, 69% for fluoxetine therapy (*P*=.01 vs combination), and 65% for CBT (*P*=.002 vs combination). At 36 weeks, no significant differences were noted; response rates were 86% for combination therapy, 81% for fluoxetine therapy, and 81% for CBT. Fluoxetine alone resulted in more suicidal ideation compared with CBT alone (14% vs 3.9%; *P*=.04) and compared with CBT plus fluoxetine (2.5%; *P*=.04) at 36 weeks.[2] EBP

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1. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al; for the Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004; 292(7):807–820. **[STEP 2]**
2. March JS, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al. The Treatment for Adolescents with Depression Study (TADS): long-term effectiveness and safety outcomes. *Arch Gen Psychiatry*. 2007; 64(10):1132–1143. **[STEP 2]**

GLOSSARY

ARR=absolute risk reduction
CDC=Centers for Disease Control and Prevention
CI=confidence interval
CT=computed tomography
FDA=US Food and Drug Administration
HR=hazard ratio
LOE=level of evidence
MRI=magnetic resonance imaging
NNH=number needed to harm
NNT=number needed to treat
NSAID=nonsteroidal anti-inflammatory drug
OR=odds ratio
RCT=randomized controlled trial
RR=relative risk
SOR=strength of recommendation
SSRI=selective serotonin reuptake inhibitor
WHO=World Health Organization

Maternal fish oil supplementation to prevent asthma in children

Bisgaard H, Stokholm J, Chawes BL, et al. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. *N Engl J Med*. 2016; 375(26):2530–2359.

This double-blind, parallel-group RCT from a Danish birth cohort assessed the risk of persistent wheeze and asthma in the offspring of 736 pregnant women receiving fish oil (n-3 long-chain polyunsaturated fatty acids [LCPUFAs]) compared with placebo (olive oil). Women took 2.4 g/d N-3 LCPUFA (55% eicosapentaenoic acid [EPA] and 37% docosahexaenoic acid [DHA]) or placebo starting at week 24 of pregnancy and continued until 1 week postpartum between November 2008 and November 2010.

Analyses for the primary outcome of persistent wheeze or asthma and secondary outcomes of lower respiratory tract infections, asthma exacerbations, eczema, and allergic sensitization in the offspring (N=695) were conducted at 3-year (double-blinded) and 5-year (investigator blinded) follow-up.

Fewer children whose mothers received fish oil had persistent wheeze or asthma compared with placebo (17% vs 24%; hazard ratio [HR] 0.69; 95% CI, 0.49–0.97; number needed to treat [NNT]=15). Additionally, children of supplemented mothers with the lowest blood levels of EPA and DHA at randomization experienced the greatest benefit and were diagnosed with persistent wheeze or asthma significantly less than placebo (18% vs 34%; HR 0.46; 95% CI, 0.25–0.83; NNT=6). No significant differences were seen in children of mothers with the middle and highest third of DHA and EPA levels.

The only risk reduction for secondary endpoints was found with infections of the lower respiratory tract (32% vs 39%; HR 0.75; 95% CI, 0.58–0.98). No serious adverse effects of fish oil or placebo were reported in the study.

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

Bottom line: Fish oil supplementation for pregnant women during the third trimester is safe and beneficial to reduce the risk of persistent wheeze and asthma in children through 5 years of age. Whereas such supplementation was beneficial overall, it appears to be most beneficial for women with low levels of DHA and EPA.

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Dabigatran or rivaroxaban for nonvalvular atrial fibrillation?

Graham DJ, Reichman ME, Wernecke M, Hsueh YH, Izem R, Southworth MR, et al. Stroke, bleeding, and mortality risks in elderly Medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. *JAMA Intern Med*. 2016; 176(11):1662–1671.

This retrospective study included 118,891 patients 65 years old or older enrolled in fee-for-service Medicare who had nonvalvular atrial fibrillation and were started on either standard-dose dabigatran or standard-dose rivaroxaban. The mean duration of follow-up was 4 months.

No statistically significant difference was found in the numbers of thromboembolic stroke (hazard ratio [HR] 0.81; 95% CI, 0.65–1.0) or mortality (HR 1.2; 95% CI, 1.0–1.3) between the groups. The rivaroxaban group had a statistically significant increase in intracranial hemorrhage (HR 1.7; 95% CI, 1.2–2.3), major extracranial bleeding (HR 1.5; 95% CI, 1.3–1.7), and major gastrointestinal bleeding (HR 1.4; 95% CI, 1.2–1.6).

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

Bottom line: In patients with nonvalvular atrial fibrillation for whom anticoagulation with a novel oral anticoagulant is desired, standard-dose dabigatran is as effective as and safer than standard-dose rivaroxaban during the initial months of treatment. Whether this advantage disappears beyond 4 months is unknown.

Additionally, this study does not address the relative safety and efficacy of these medications compared with warfarin or other available novel oral anticoagulants. Therefore, this study does not provide a definitive answer as to which anticoagulation agent should be the treatment of choice for nonvalvular atrial fibrillation. EBP

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