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EVIDENCE-BASED PRACTICE

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Family Physicians Inquiries Network

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The new desk job

I sit a lot. I sit when I am editing this journal. I sit when I am filling out resident performance evaluations, when writing letters of recommendation, and when writing clinic notes. I sit when I watch TV, when I commute, when I eat. Sometimes I use walking to simply go from 1 chair to another. I judge the quality of a chair by how long I can sit in it before having to move.

Apparently, I am not unique in this routine. Sitting has become the new American pastime. Sitting is what you do to interact with your computer, the driver of world economies. Unfortunately, several studies have now linked the somewhat oxymoronic "activity of sitting" to poor health. Well, that's not much of a surprise.

The surprise is what we conjure up to deal with this state of affairs. We have things we can put on our wrists that count our steps, upload the data to the cloud, and allow us to see how far we walked . . . *when we are next seated at our computers!* We have Pilates and Zumba and Barre and boot camps and hot yoga and step aerobics classes that we drive to after work. Few people seem to realize that we might benefit as much by simply walking home from work.

Also popular now is the mechanical desk that moves up and down. The rationale seems to be that if sitting is bad, standing will be less bad. A group at the Cochrane Library decided to see if "sit-stand" desks had any effect. They identified 6 studies of these desks (with some form of randomization) with 218 participants.[1] Sit-stand desks reduced time sitting at work somewhere between 30 minutes and 2 hours at 3-month follow-up. That's not bad until you realize that the numbers were small, the follow-up short, the study quality low, and the outcome was not a health measure.

But weak evidence has not stopped sit-stand desks from popping up everywhere. My clinic partner even put one in. I hit my knee on the weirdly cantilevered thing every time I try to sit down.

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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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Do canalith repositioning exercises at home improve symptoms of benign paroxysmal positional vertigo?

EVIDENCE-BASED ANSWER

After a 1-time physician-administered Epley maneuver, adding a week of self-administered Epley maneuvers at home increases the likelihood of a negative Dix-Hallpike test by 30%, but does not lead to more patients with complete resolution of vertigo symptoms. Self-treatment with a modified Epley maneuver at home is 60% more likely than a modified Semont maneuver, and nearly 3 times more likely than Brandt-Daroff exercises to abolish symptoms of benign paroxysmal positional vertigo (BPPV) (SOR: **B**, RCTs and cohort study).

Evidence summary

A 2005 RCT in Japan compared a 1-time physician-administered modified Epley maneuver with a 1-time physician-administered Epley maneuver plus home self-treatment with modified Epley maneuvers up to 3 times daily for the treatment of BPPV.[1] (The modified Epley maneuver does not include vibrations of the mastoid process originally advocated by Epley and is more applicable to home use.) Participants (N=80) with a median age of 64 years and a median duration of symptoms of 10 days were randomly assigned to both groups. Follow-up at 1 week measured the following outcomes: complete resolution of symptoms, negative Dix-Hallpike, and resolution of symptoms plus a negative Dix-Hallpike.

A negative Dix-Hallpike was noted in 90% of the home-treatment group versus 72% in the office-treatment group (risk ratio [RR] 1.3; 95% CI, 1.0–1.6). Complete resolution of positional vertigo, although not significantly different between groups, was achieved in 88% in the home-treatment group versus 77% in the office-treatment group (RR 1.1; 95% CI, 0.92–1.4). Similarly, no difference was noted in the combined negative Dix-Hallpike and complete resolution outcome: 88% in the home-treatment group versus 69% in the office-treatment group (RR 1.3; 95% CI, 0.99–1.6).[1]

A 2004 RCT (N=70) compared self-treatment with either a modified Semont maneuver or a modified Epley maneuver for posterior canal BPPV.[2] The modified Semont maneuver was adapted from the original Semont maneuver and decreases the time the head is held in the stimulus position. Maneuvers were performed once under supervision in the clinic and then 3 times daily until positional vertigo had ceased for at least 24 hours. Follow-up occurred 1 week after treatment, and response was defined as an absence of positional vertigo and torsional/upbeating nystagmus on positional testing.

At follow-up, 95% of patients in the modified Epley maneuver group had vertigo resolution, compared with 58% in the modified Semont maneuver group (RR 1.6; 95% CI, 1.2–2.2). The higher failure rate with the modified Semont maneuver was attributed to incorrect performance, whereas deviations from the step-wise modified Epley maneuver did not adversely affect outcomes.[2]

A 1999 prospective cohort study (N=54) compared the modified Epley maneuver with Brandt-Daroff exercises for self-treatment of BPPV.[3] Maneuvers were performed once under supervision and then 3 times daily until positional vertigo symptoms had subsided for 24 hours. The Brandt-Daroff exercise is a form of habituation exercise, designed to allow the patient to become accustomed to the positions which cause the vertigo symptoms.

At 1-week follow-up, 64% of patients using the modified Epley maneuver had resolution of symptoms compared with 23% using the Brandt-Daroff exercises (RR 2.8; 95% CI, 1.3–5.9). A limitation to this study was lack of randomization, in which patients who had tried Brandt-Daroff exercises in the past and failed were specifically referred for Epley maneuver.[3] EBP

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Effective method to obtain urine from infants

Kaufman J, Fitzpatrick P, Tosif S, Hopper SM, Donath SM, Bryant PA, et al. Faster clean catch urine collection (Quick-Wee method) from infants: randomised controlled trial. *BMJ*. 2017; 357:j1341.

This nonblinded RCT compared 2 methods for obtaining a clean-catch urine sample within 5 minutes from 354 infants aged 1 to 12 months presenting to an Australian pediatric emergency room. After clinicians determined that clean-catch urine was needed, patients were randomized to the Quick-Wee method (suprapubic stimulation with gauze soaked in cold fluid) or usual care (waiting for spontaneous voiding with no stimulation). The most common reasons to obtain urine were fever of unknown origin and "unsettled baby."

The primary outcome was voiding within 5 minutes and secondary outcomes included contamination rate and parent/clinician satisfaction.

Using the Quick-Wee method, 30% of patients provided a successful clean catch sample within 5 minutes compared with 9% in the usual-care group (95% CI, 3.4–7.7; *P*<.001; number needed to treat=4.7). Contamination rates were no different between Quick-Wee and usual-care samples. Both parents and clinicians were more satisfied with the Quick-Wee method than usual care (median score of 2 vs 3 on a 5-point Likert scale, in which 1 is most satisfied; *P*<.001).

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

Bottom line: Using gauze soaked in cold fluid to stimulate a urine sample from infants aged 1 to 12 months produces significantly more clean-catch urine samples than simply waiting for the patient to void, with no difference in contamination and increased parental and provider satisfaction. For patients with whom clean-catch urine is appropriate, try this technique first!

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Tamsulosin is beneficial for distal, larger stone (5–10 mm) passage

Wang RC, Smith-Bindman R, Whitaker E, Neilson J, Allen IE, Stoller ML, et al. Effect of tamsulosin on stone passage for ureteral stones: a systematic review and meta-analysis. *Ann Emerg Med*. 2017; 69(3):353–361.e3.

This meta-analysis of 8 RCTs of adult patients (N=1,384) examined if ureteral stone size modified the effect of oral tamsulosin 0.4 mg daily (average of 28-day course) on the rate of distal ureteral stone passage. Included studies were published from 1966 to 2015, from multiple countries, and in both emergency department and outpatient settings, regardless of language. Secondary outcomes were postural hypotension and dizziness.

The pooled risk of stone passage was higher in the tamsulosin group than the placebo group, but significant heterogeneity existed across trials (85% vs 66%; *P*<.001; I^2=80.2%). After subgroup analysis by stone size, tamsulosin was beneficial for larger stones, 5 to 10 mm (n=514, risk difference 22%; 95% CI, 12%–33%, number needed to treat=5) compared with placebo.

The subgroup analysis for smaller stones (<4 to 5 mm) indicated no benefit (n=533, risk difference –0.3%; 95% CI, –4% to 3%), likely due to the high rate of spontaneous stone passage for smaller stones. Tamsulosin did not increase the risk of dizziness or postural hypotension.

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

Bottom line: In patients with distal ureteral stones measuring 5 to 10 mm, tamsulosin 0.4 mg once daily for 28 days significantly improves stone passage without increasing the risk for dizziness or postural hypotension. EBP

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

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Does screening for trichomonas in pregnancy improve outcomes?

CASE

A 23-year-old woman presents to your office for her first prenatal visit at 15 weeks 2 days gestational age by last menstrual period. She reports that a friend of hers was recently treated for trichomonas during pregnancy. She asks if she should be screened for trichomonas.

Bottom line

Screening for trichomonas, candida, and bacterial vaginosis, along with treatment of positive tests, reduces the risk of preterm birth and preterm low birth weight. HIV vertical transmission can also be reduced by screening for and treating trichomonas, bacterial vaginosis, and candida in HIV-infected pregnant women. However, the current guidelines from the Centers for Disease Control and Prevention (CDC) recommends screening only for trichomonas in HIV-infected pregnant women.

Review of the evidence

A 2015 systematic review found 1 RCT (N=4,155) meeting inclusion criteria that examined the effect of lower genital tract infection screening and treatment on preterm labor and preterm low birth weight.[1] Asymptomatic women with a singleton pregnancy at a gestational age between 15 weeks 0 days and 19 weeks 6 days were randomized to screen and treat for candida, bacterial vaginosis, and trichomonas versus screening but no treatment.

The rate of preterm birth before 37 weeks' gestation was significantly lower in the intervention group (risk ratio [RR] 0.55; 95% CI, 0.41–0.75). The intervention group had significantly fewer infants born preterm with low birth weight of ≤2,500 g (RR 0.48; 95% CI, 0.34–0.66) and very low birth weight of ≤1,500 g (RR 0.34; 95% CI, 0.15–0.75).[1]

A 2015 retrospective cohort study found that the incidence of preterm birth was significantly lower in the intervention group in which a screen and treat program for lower genital tract infection was implemented.[2] In this study, women with a high-risk singleton pregnancy who presented for prenatal care between 10 and 16 weeks' gestation who agreed to screen and treat for candida, bacterial vaginosis, and trichomonas (n=8,490) were compared with a control group of women with high-risk singleton pregnancies who did not undergo the screen and treat program (n=8,651).

The intervention group had a preterm birth rate of 9.7% (95% CI, 9.0–10.3) compared with 22% (95% CI, 21–23) in the control group. Few patients had trichomonas, and conclusions could not be drawn regarding screening and treatment for trichomonas alone.[2]

The above studies examined women with no other infectious comorbidities. In 2010, an observational cohort study assessed rate of HIV vertical transmission up to 15 months after delivery in HIV-infected women enrolled at a primary maternal child health clinic in Harare, Zimbabwe.[3] Lower genital tract infections imparted a risk ratio of 2.04 (95% CI, 1.37–3.04) for HIV vertical transmission.

Recommendations from others

The 2015 treatment guidelines for STDs from the CDC[4] recommended routine screening for trichomonas in HIV-infected women and cited the observational cohort study from Zimbabwe. The guidelines state that screening for trichomonas in otherwise healthy women did not have established benefit.

A limitation of the studies was that they evaluated lower genital tract infections including trichomonas, but did not examine the effect of trichomonas alone.

CASE WRAP-UP

You and the patient decide to screen for HIV and lower genital tract infections, to reduce the risk of HIV vertical transmission and preterm birth. EBP

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How long should antibiotic therapy be continued for an uncomplicated UTI in an elderly woman?

EVIDENCE-BASED ANSWER

In older adult women with uncomplicated lower urinary tract infections (UTIs), 3- to 6-day antibiotic regimens result in less persistence than single-dose treatments and have similar outcomes to longer regimens (SOR: **A**, meta-analysis of RCTs). A 3-day antibiotic course is recommended for uncomplicated symptomatic lower UTIs in women, including women older than 64 years (SOR: **A**, evidence-based guideline).

A 2008 meta-analysis of 15 RCTs (N=1,644) compared the effectiveness of single-dose, short-course (3–6 days), and long-course (7–14 days) antibiotic therapy for uncomplicated, symptomatic lower UTI in women aged 60 years or older.[1] Symptomatic lower UTI was defined as symptoms of dysuria, urgency, frequency, or suprapubic pain with positive urine culture and pyuria. Outcomes were persistent UTI at short-term (positive urine culture <2 weeks posttreatment) and long-term (positive urine culture >2 weeks posttreatment) follow-up, clinical failure (persistence of symptoms), and rate of adverse drug reactions. The quality of this meta-analysis was affected by heterogeneity: the term "elderly" was defined differently in the studies (7 of 15 studies included patients between ages of 50 and 60), different antibiotics were studied (sulfamethizole, trimethoprim, fosfomycin, cephalexin, and fluoroquinolones), and 8 of 15 studies compared different antibiotics for different durations.

Single-dose treatment compared with short-course treatment resulted in a higher rate of persistent UTI at short-term (5 trials, n=356; risk ratio [RR] 2.0; 95% CI, 1.1–3.8) and a similar rate of persistent UTI at long-term (3 trials, n=95; RR 1.2; 95% CI, 0.59–2.3) follow-up. The comparison of single-dose treatment with long-course treatment yielded similar results: the rate of persistent UTI was higher at short-term (6 trials, n=628; RR 1.9; 95% CI, 1.0–3.7) and similar at long-term (5 trials, n=523; RR 1.3; 95% CI, 0.89–1.8). Pooling 3 trials (n=595) showed no difference in adverse reactions between single-dose and long-course treatment. Short-course treatment and long-course treatment resulted in similar rates of persistent UTI at short-term and long-term follow-up, rates of clinical failure, and adverse reactions.[1]

The 2008 American Congress of Obstetricians and Gynecologists' evidence-based practice bulletin on treatment of UTI in nonpregnant women concluded that single-dose treatment of symptomatic lower UTI was not as effective as longer courses, and stated that a 3-day course was as effective as and better tolerated than a 7-day regimen.[2] They recommend 3 days of antibiotic treatment for uncomplicated UTI in women, including women older than 64 years old (Level A: good and consistent scientific evidence).

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What is the best approach for immunocompetent patients with a positive skin and a negative blood test for tuberculosis (TB)?

EVIDENCE-BASED ANSWER

Patients with a positive tuberculin skin test (TST) and a negative interferon-gamma release assay (IGRA) may be approached as if they have a negative skin test alone, because the risk of progression to active disease is the same or lower (SOR: **B**, prospective cohort studies). Expert opinion guidelines do not provide specific recommendations for managing discordant TST and IGRA results.

A 2015 Spanish prospective diagnostic cohort study followed close contacts of active TB cases (N=1,311) over 4 years for the development of active TB.[1] Contacts received initial TST and IGRA testing without treatment. The study was performed in a low TB incidence country, but included 58% immigrants, and 67% of patients had received Bacillus Calmette–Guérin (BCG) vaccine.

Of 514 patients with a negative TST, 3 developed active TB for a sensitivity of 96%, a specificity of 42%, positive predictive value (PPV) 9.6%, and a negative predictive value (NPV) 99.4%, with a positive likelihood ratio (LR+) of 1.65 and a negative likelihood ratio (LR–) of 0.10. Of the 346 patients with a positive TST and a negative IGRA, active TB developed in 4 (1.2%), for a sensitivity of 94.8%, a specificity of 47.5%, PPV 16.2%, NPV 98.8%, LR+ 1.81, and LR– 0.11.[1]

A 2011 German prospective diagnostic cohort study followed close contacts of patients with active TB (N=1,414) for at least 2 years for the development of active TB.[2] Contacts received a TST and IGRA test at enrollment and 954 patients were observed for at least 2 years without treatment (median duration 3.5 years). The study was performed in a low TB incidence country, but 40.6% of patients were foreign born and 51.9% had received BCG vaccine.

Of 350 patients with a negative TST, 2 patients (0.6%) developed active TB, for a sensitivity of 63.6%, a specificity of 36.8%, PPV 2.5%, NPV 99.4%, LR+ 1.46, and LR– 0.99. Of the 413 patients with a positive TST and a negative IGRA, no patients (0%) developed active TB, for a sensitivity of 100%, a specificity of 69.9%, PPV 8.8%, NPV 100%, LR+ 1.41, and LR– 0.[2]

The 2010 expert-opinion guidelines from the Centers for Disease Control and Prevention for testing at-risk individuals aged 5 years and older for risk of development of TB did not recommend simultaneous use of TST and IGRA, but did recommend using IGRA in patients who had received BCG, were unlikely to return for reading of a TST, or if the initial TST test was positive in patients at low risk for infection and progression to active TB.[3] These guidelines recommended individualizing decisions about discordant results based on "the quality and magnitude of each test result, the probability of infection, the risk for disease if infected, and the risk for a poor outcome if disease occurs."

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Does the use of a lubricant during a Pap smear decrease the accuracy of the test result?

EVIDENCE-BASED ANSWER

Lubrication of the speculum does not change the rate of unsatisfactory cytology in specimens collected using the conventional Pap smear method (SOR: **A**, meta-analysis of RCTs and quasi-randomized trials). Carbomer-containing lubricant increases unsatisfactory cervical cytology in specimens collected using liquid-based Pap smears methods, while noncarbomer lubricants have no effect (SOR: **B**, retrospective cohort study).

A meta-analysis of 5 randomized trials and 2 quasi-randomized trials (N=8,717) evaluated the effect of speculum lubrication with water-based gels on Pap smear cytology results.[1] In the included studies, 4,450 (51%) Pap smears were done with a lubricated speculum and 4,267 (49%) with a nonlubricated speculum. Lubrication techniques varied from gel applied only to the speculum tip or to the entire length.

For Pap smears using conventional cytology, no difference was noted in unsatisfactory results between procedures performed with or without lubricated speculums (6 trials, n=8,398; odds ratio [OR] 0.94; 95% CI, 0.64–1.4). The authors noted that nonrandomized and uncontrolled studies using liquid-based cytology not included in this meta-analysis raised the possibility of interference of results by lubricants.[1]

A retrospective cohort study evaluated all liquid-based Pap tests collected between January 2010 and March 2012 by the Gynecologic Oncology division at a single hospital.[2] Overall, 2,041 liquid-based cervical Pap smears were collected during the study period, of which 675 involved speculum lubricant and 1,366 did not. Lubrication standard practice was described as a dime-sized amount of lubricant on the speculum.

During the sixth through eighth quarters of the study, a large increase in unsatisfactory results was noted, correlating with a change to a carbomer-containing lubricant. Specimens collected with a carbomer-based water-soluble lubricant (n=223) had an unsatisfactory cytology rate of 3.6% versus 0.9% with a noncarbomer lubricant (n=452) used during

quarters 1 through 5 and 9 (OR 4.1; 95% CI, 1.2–14) and 0.4% with no lubricant (OR 8.4; 95% CI, 2.9–24). No difference was noted in unsatisfactory cytology when using a noncarbomer lubricant versus no lubricant (*P*=.28).[2]

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In adults with community-acquired pneumonia (CAP), are corticosteroids beneficial?

EVIDENCE-BASED ANSWER

Yes. In patients with severe CAP, corticosteroids reduce mortality, length of hospital stay, need for mechanical ventilation, development of adult respiratory distress syndrome (ARDS), and time to clinical stability (SOR: **A**, meta-analysis of RCTs). Corticosteroids show better efficacy in patients with severe CAP and septic shock than in patients with CAP but no shock (SOR: **B**, large cohort study).

A 2015 systematic review and meta-analysis of 13 RCTs (N=2,005) evaluated the benefits of systemic corticosteroids, compared with placebo or no treatment, in hospitalized adults (mean age 60 years) with CAP.[1] Outcomes included length of hospital stay, time to clinical stability, all-cause mortality, need for mechanical ventilation, or development of ARDS. Corticosteroids included intravenous or oral dexamethasone, prednisone, prednisolone, methylprednisolone, or hydrocortisone.

All-cause mortality was similar in the corticosteroid group compared with control (5.3% vs 7.9%; 12 trials, n=1,954; RR 0.67; 95% CI, 0.45–1.01). However, when limited to patients with severe pneumonia (using validated pneumonia severity scales), a statistically significant benefit was observed with corticosteroids (6 trials, n=388; RR 0.39; 95% CI, 0.20–0.77). Significant benefits from corticosteroids included need for mechanical ventilation (5 trials, n=1,060; RR 0.45; 95% CI, 0.26–0.79); length of stay (3 trials, n=1,288; mean difference –1.0 day; 95% CI, –1.8 to –0.21); time to clinical stability marked by normal vital signs and no supplemental oxygen (5 trials, n=1,180; mean difference –1.2 days; 95% CI, –2.1 to –0.35); and risk for ARDS (4 trials, n=945; RR 0.24; 95% CI, 0.10–0.56).[1]

A 2015 cohort study (N=6,925) evaluated the efficacy of low-dose corticosteroids for reducing 28-day mortality in patients with severe CAP.[2] Inclusion criteria included age older than 18 years, current diagnosis of CAP, with antibiotics started on day 0 or 1; and required mechanical ventilation within 7 days of admission. Low-dose corticosteroids were defined as methylprednisolone 0.5 to 2.5 mg/kg per day or equivalent dose of hydrocortisone, prednisolone, betamethasone or dexamethasone. Exclusion criteria included corticosteroids for fewer than 3 days; no corticosteroids within 7 days of admission; or use of high-dose corticosteroids. Results were evaluated for matched (by logistic regression with 19 variables) and unmatched groups. The unmatched group included all patients selected.

The 28-day mortality rate was significantly lower in patients with CAP with septic shock (requiring catecholamines within 7 days of admission) who received corticosteroids in both unmatched (steroid n=631, control n=1,893; 25% vs 36%; *P*<.001) and matched (steroids n=491, control n=189; 25% vs 33%; *P*=.01) patients. Overall reduction in 28-day mortality associated with corticosteroid use was 27% (95% CI, 13–42).[2]

In patients with CAP without septic shock, a significant difference in mortality was observed between unmatched groups (steroid n=1,112, control n=3,289; 16% vs 19%; *P*=.01). No difference was seen between matched groups (n=943 each; 18% vs 16%; *P*=.22). Corticosteroids showed no overall reduction in 28-day mortality in CAP without septic shock (3.0% reduction; 95% CI, –7.6 to 14).[2]

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What is the optimal dosing of lisinopril for renal protection in normotensive patients with diabetes and moderate albuminuria (30–299 mg/d)?

EVIDENCED-BASED ANSWER

Lisinopril dosed at least 10 mg daily decreases risk for progression from micro- to macroalbuminuria in patients with cardiovascular risk factors including diabetes (SOR: **B**, meta-analysis of RCTs). In insulin-dependent patients with microalbuminuria, lisinopril 10 to 40 mg daily (titrated to lower diastolic pressures <75 mmHg) decreases albumin excretion rates (SOR: **C**, extrapolated from an RCT in which patients had normal-range blood pressures and modest systolic hypertension).

A 2011 meta-analysis of 85 RCTs (N=21,708) evaluated multiple angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapies versus placebo or a combination of ACEI and ARB for multiple endpoints in patients with cardiovascular risk factors including type 1 and type 2 diabetes.[1] Definitions of albuminuria varied. A subgroup of 3 RCTs studied lisinopril dosed at least 10 mg daily compared with placebo in patients with microalbuminuria (N not given).

Lisinopril use decreased progression from micro- to macroalbuminuria (relative risk [RR] 0.33; 90% CI, 0.13–0.85.) No studies included a lisinopril dose less than 10 mg daily. The number of patients who had diabetes or also had hypertension was unclear.[1]

A 1997 double-blinded multicenter RCT of 530 normotensive (resting blood pressure: systolic <155 mmHg and diastolic between 75 and 90 mmHg) patients with insulin-dependent diabetes evaluated lisinopril versus placebo to slow the progression of urinary albumin excretion.[2] This RCT was included in the meta-analysis above, but provides data specific to normotensive patients taking lisinopril. Exclusion criteria included a history of renal or cardiovascular disease, proteinuria of more than 250 µg/min, hematuria, or patients taking blood pressure medications. Lisinopril was started at 10 mg daily and titrated to achieve a target diastolic pressure of less than 75 mmHg.

At 24 months, patients receiving lisinopril had a 19% lower albumin excretion rate than patients taking placebo (95% CI, 2–33; *P*=.03). No patients in the treatment group received less than 10 mg lisinopril.[2]

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

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Should a provider advise patients against the consumption of high-concentration fructose products?

EVIDENCE-BASED ANSWER

Fructose consumption has no clinically significant short-term effects on high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, blood pressure, or body weight (SOR: **C**, meta-analyses of disease-oriented evidence). None of these studies evaluated long-term effects or patient-oriented outcomes.

A 2015 meta-analysis of 59 randomized and nonrandomized crossover and parallel studies (N=1,068) assessed the effect of fructose on serum HDL, triglyceride, and LDL-C levels compared with nonfructose carbohydrates in controlled feeding trials.[1] The studies were conducted predominantly in an outpatient setting in the United States and Europe. The median age of patients in the 51 isocaloric studies (n=943) was 40 years with a 1:1 ratio of men to women.

Isocaloric fructose administration was not associated with a significant change in serum HDL levels (28 studies, n=762; mean difference [MD] 0.00 mmol/L; 95% CI, –0.04 to 0.04), serum triglyceride levels (51 studies, n=356; MD 0.01 mmol/L; 95% CI, –0.05 to 0.08), or serum LDL levels (26 studies,

n=158; MD 0.03 mmol/L; 95% CI, –0.05 to 0.11) in comparison to nonfructose carbohydrate diets.[1]

Furthermore, the 8 hypercaloric studies (n=125) that furnished 24% to 35% excess fructose caloric intake found no correlative alterations in serum HDL levels (4 trials, n=46; MD 0.05 mmol/L; 95% CI, –0.07 to 0.17) or serum LDL-C levels (4 trials, n=46; MD 0.08 mmol/L; 95% CI, –0.22 to 0.38). Hypercaloric trials did demonstrate a tiny increase in serum triglyceride levels (8 studies, n=218; MD 0.26 mmol/L; 95% CI, 0.11–0.41).[1]

A 2014 meta-analysis of 3 prospective cohort studies (with 37,375 men and 185,855 women) investigated the relationship between self-reported fructose-containing sweetener intake and incident hypertension.[2] No association was found between fructose intake and hypertension when fructose constituted 14% or more of the total energy intake (RR 1.0; 95% CI, 0.99–1.0).

A 2012 meta-analysis of 41 prospective cohort studies evaluated alterations in body weight when participants adhered to controlled isocaloric (31 studies, n=637) and hypercaloric (10 studies, n=119) feeding trials comparing fructose with nonfructose carbohydrates.[3] The studies were small (<15 participants) and short-term (<12 weeks' duration). Studies that compared the effect of supplemental free, unbound fructose with other carbohydrates were included. Studies with trials lasting fewer than 7 days were excluded. The median age of participants was 43 years in the isocaloric studies and 25 years in hypercaloric studies.

Isocaloric studies found no significant change in weight (31 studies, n=637; MD –0.14 kg; 95% CI, –0.37 to 0.10), but excess fructose administration in hypercaloric trials (104–250 g/d, 18%–97% of total energy intake) was associated with a small weight increase (10 studies, n=119; MD 0.53 kg; 95% CI, 0.26–0.79).[3]

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What are the risks with corticosteroid injections for plantar fasciitis?

EVIDENCE-BASED ANSWER

Pain with injection is the most common reported adverse event from corticosteroid injections for plantar fasciitis, with 13% to 100% of study patients reporting pain (SOR: **B**, systematic reviews of RCTs with incomplete reporting). Corticosteroid injections are associated with plantar fascia rupture in 2.4% of patients after a mean of 2.7 injections (SOR: **B**, retrospective cohort study).

A 2016 systemic review of 22 RCTs (N=1,216) evaluated the efficacy of various injection therapies for plantar fasciitis (fibromatosis).[1] Of the 1,216 included patients, 430 received corticosteroid injections (data obtained from the author), but the number of trials these 430 patients participated in was unknown. Patients ranged from 37 to 57 years old.

Sixteen studies reported an absence of serious adverse events. The other 6 studies did not mention adverse events. Fifty-six patients (13%) who received corticosteroids reported painful injections and 4 patients reported postinjection pain requiring treatment with analgesics. The number of patients in the placebo groups reporting painful injections was not provided. No other minor adverse events were reported.[1]

A 2015 systemic review of 10 RCTs (N=622) addressed the effectiveness of corticosteroid injections for plantar fasciitis.[2] Patients were 41 to 57 years old; most patients had had symptoms for at least 6 months.

Six studies (n=351) reported an absence of adverse events. One study reported painful injections in all patients in both treatment and control groups in the study (n=64), with no other adverse events reported. Three studies (n=207) did not comment on adverse events. Only 1 study had a follow-up time longer than 6 months. This may result in underreporting of delayed complications. Five of the 7 studies that reported no observed adverse events were also included in the 2016 systemic review described above.[2]

A 2010 retrospective cohort analysis (N=120) addressed the incidence of plantar fascia rupture after corticosteroid injection.[3] The study reviewed random charts for patients diagnosed with plantar fasciitis between January 2007 and January 2008. All patients received injections of mixed

lidocaine, bupivacaine, dexamethasone, and triamcinolone. Patients received an average of 2.1 injections with an average interval of 3.7 months between injections.

Three patients (2.5%) had confirmed plantar fascia rupture by MRI after receiving 5, 2, and 1 injections, respectively, with an average injection interval of more than 3.7 months. Patients with a confirmed rupture averaged 2.7 injections versus 2.1 injections in patients without a rupture (no statistical analysis reported). All 3 ruptures occurred in middle-aged women, with a body mass index of more than 30 kg/m^2, who were actively walking or jogging at the time of rupture. This study was limited by its use of a specific treatment protocol with limited generalizability.[3]

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Does physical activity in children with attention deficit hyperactivity disorder (ADHD) improve symptoms or decrease medication use?

EVIDENCE-BASED ANSWER

Physical activity in children and teenagers with ADHD leads to moderate to large improvements in ADHD symptoms (SOR: **A**, meta-analysis of RCTs). However, physical activity is not associated with a significant decrease in ADHD medication use (SOR: **B**, single cohort study).

A 2015 meta-analysis of 8 RCTs examined the effect of exercise on ADHD symptoms in 249 children and adolescents (6–18 years old, mean age 10.6 years).[1] The exercise interventions were heterogeneous in type, duration, frequency, and intensity. The outcome measures varied among the studies, so results were reported as standardized mean differences (SMD).

Aerobic exercise significantly decreased core ADHD symptoms. A large effect was found on attention (5 trials, n=142; SMD 0.84; 95% CI, 0.48–1.2) and moderate effects were found on hyperactivity (2 trials, n=62; SMD 0.56; 95% CI, 0.04–1.1), impulsivity (2 trials, n=62; SMD 0.56; 95% CI, 0.04–1.1), anxiety (2 trials, n=64; SMD 0.66; 95% CI, 0.13–1.2), executive function (3 trials, n=102; SMD 0.58; 95% CI, 0.15–1.0), and social disorders (2 trials, n=53; SMD 0.59; 95% CI, 0.03–1.2).[1]

A 2010 cohort study of 1,214 second through fourth graders evaluated structured bursts of physical activity on student fitness levels and medication use for ADHD and asthma.[2] The structured bursts of physical activity led by teachers included a warm-up; core strength or aerobic activity such as lunges, squats, hopscotch, jogging, or dancing; and cool down for at least 30 minutes total throughout the school day. A secondary outcome evaluated ADHD medication usage (based on school nurse data) and revealed no significant difference between the intervention and control groups.

Seven of the 21 children (33%) in the intervention group who started the school year taking ADHD medication were not taking ADHD medication the following April, while 1 child of the 14 (7.1%) taking ADHD medication in the control group had the same change (P=.07).[2]

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In adults with acute bacterial meningitis caused by *Streptococcus pneumoniae*, what are the effects of corticosteroids on morbidity and mortality?

EVIDENCE-BASED ANSWER

Treatment with corticosteroids decreases mortality by 16% in patients with acute *S pneumoniae* meningitis of any age (SOR: **A**, meta-analysis of RCTs), and corticosteroids decrease the odds of the combined outcome of death or severe-to-moderate disability at discharge in adults (SOR: **B**, cohort study). In adults and children with meningitis of any cause, corticosteroids lower the rates of neurological sequelae and hearing loss, but these effects appear to be restricted to some high-income countries and are not seen in low-income countries. (SOR: **A**, meta-analysis of RCTs).

A 2015 meta-analysis (25 RCTs, N=4,121) evaluated the effect of systemic corticosteroids on morbidity and mortality from meningitis in 2,511 children and 1,517 adults and included a subgroup analysis of 1,132 cases of *S pneumoniae* meningitis.[1] Most trials enrolled patients 16 years old and older and administered dexamethasone 0.4 to 1.5 mg/kg per day for 2 to 4 days. Other corticosteroids studied were hydrocortisone (dose not reported), prednisolone (120 mg/d for 3 days), or combination therapy (hydrocortisone 100 mg for 1 day followed by 60 mg/d prednisolone). Corticosteroids were administered before or with the first dose of antibiotics in 13 trials.

For meningitis caused by *S pneumoniae* in patients of any age (17 trials, n=1,132), corticosteroid treatment compared with placebo resulted in lower mortality (30% vs 36%; relative risk [RR] 0.84; 95% CI, 0.72–0.98). Subgroup analysis by causative microorganism was not performed for morbidity measures; however, overall pooled morbidity data in patients of all ages showed corticosteroids compared with placebo resulted in lower rates of short-term focal neurological deficits such as seizures (4 trials, n=542; RR 0.83; 95% CI, 0.69–1.0), any hearing loss (3 trials, n=649; RR 0.74; 95% CI, 0.63–0.87), and bilateral hearing loss of more than 60 dB or need for hearing aids (4 trials, n=844; RR 0.67; 95% CI, 0.51–0.88).[1]

In a subgroup analysis of studies from 9 low-income countries (United Nations Human Development index <0.7) and 16 high-income countries (United Nations Human Development index >0.7), these improvements in morbidity from meningitis of any cause appeared to be exclusive to high-income countries, and corticosteroids did not show benefit in studies from low-income countries.[1]

A prospective cohort study not included in the meta-analysis above evaluated 1,412 cases of bacterial meningitis treated with antibiotics and dexamethasone or antibiotics only in patients older than 16 years old (median age 61 years).[2] Most patients (n=1,017) had bacterial meningitis caused by *S pneumoniae*. Dexamethasone was dosed at 10 mg IV every 6 hours for 4 days, starting on or before first dose of antibiotics. Antibiotics in both groups included a third-generation cephalosporin, penicillin, amoxicillin, or combination therapy with amoxicillin and a third-generation cephalosporin. Primary outcomes were mortality and unfavorable outcomes defined as an outcome score of 1 to 4 on the Glasgow Outcome Scale at the time of hospital discharge. The Glasgow Outcome Scale ranges from 1=death to 4=moderate disability and 5=mild or no disability.

In the dexamethasone-treated group with meningitis of any etiology, unfavorable outcomes were lower than in the control group (34% vs 51%; *P*<.0001). For streptococcal meningitis specifically, odds ratio [OR] of unfavorable outcomes with steroid therapy was 0.55 (95% CI, 0.38–0.80). Mortality data specific to cases caused by *S pneumoniae* were not reported. In all cases of bacterial meningitis, hearing loss was not significantly affected by dexamethasone administration (OR 1.3; 95% CI, 0.80–2.2).[2]

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Do delayed antibiotic prescriptions decrease antibiotic use for respiratory infections?

EVIDENCE-BASED ANSWER

Several techniques for delaying antibiotic prescriptions decrease the use of antibiotics for treatment of upper respiratory infections (URI) compared with immediate antibiotic prescriptions in adults and children. No difference was noted in the overall rate of antibiotic use when comparing delayed versus no antibiotic prescription, nor when comparing different methods of delayed antibiotic prescriptions (SOR: **A**, systematic review of RCTs and single RCT).

A 2016 systematic review that included 88 RCTs, 40 observational studies, and 5 systematic reviews evaluated appropriate antibiotic prescribing strategies in adults and children with acute bronchitis, acute otitis media, pharyngitis, rhinitis, sinusitis, cough, or common cold.[1] Six RCTs (N=1,664) studied delayed prescribing compared with immediate prescribing. In the delayed antibiotic prescription groups, clinicians instructed patients to delay filling prescriptions, wrote postdated prescriptions, left prescriptions for later collection, or required a return visit for antibiotic prescription. Actual antibiotic use was measured in multiple ways, including diaries and prescription fill records.

Delayed antibiotic prescription resulted in antibiotic use 33% to 40% of the time. This rate represented a 34% to 76% reduction in antibiotic use compared with immediate antibiotic prescription (6 RCTs, n not given). The largest effect was seen when patients were required to return to clinic for antibiotic prescriptions, leading to a 63% to 76% reduction in antibiotic use (4 RCTs, n=1,389).[1]

When patients were given a prescription and instructed to delay treatment, there was a 34% to 49% reduction in antibiotic use (2 RCTs, n=667). However, no difference was noted in antibiotic use among the various methods of delaying prescriptions when they were compared directly. Patient satisfaction (satisfied or very satisfied) was lower in the delayed antibiotic group (5 trials, n=1,334; 85% vs 95%; OR 0.52; 95% CI, 0.35–0.76). The analysis was limited by the inclusion of various methods of delayed prescription and variability in study rigor (2 trials graded as "good" and 3 as "fair").[1]

A 2014 RCT (N=889) estimated the effectiveness of different strategies of delayed antibiotic prescription compared with no antibiotic prescription in children and adults presenting to 25 primary care clinics with URIs (common cold, influenza, pharyngitis, otitis media, sinusitis, croup, or lower respiratory infection).[2] Patients 3 years old or older were eligible; the average age was 21 years (61% female). Patients with URI who insisted on antibiotics (37%, n=333) were allocated to the immediate antibiotics. The rest (63%) were randomized to 5 methods of delayed prescriptions: instruction to delay filling, prescription left for collection, postdated prescription, recontact requirement, or no prescription. Patients completed a symptom diary and medication logs and were followed for at least 1 month to determine the primary outcome of symptom severity.

Antibiotic use was significantly less in the delayed antibiotic group than the nonrandomized immediate antibiotic group (34% vs 97%; relative risk [RR] 0.35; 95% CI, 0.31–0.40), as was belief in antibiotic effectiveness (71% vs 93%; RR 0.76; 95% CI, 0.70–0.84). No significant difference was noted in antibiotic use among the 5 antibiotic delay strategies, ranging from 26% for no antibiotic to 39% for instructions to delay filling (*P*=.29) and no difference was noted in symptom duration and severity.[2]

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Do regular family dinners decrease the incidence of obesity in adolescent patients?

EVIDENCE-BASED ANSWER

The frequency of family meals during childhood and adolescence is correlated with a lower risk of being overweight, and is also associated with lower odds of being overweight and obese in adulthood (SOR: **B**, meta-analysis of observational studies and a single cohort study). This effect holds for non-Hispanic white adolescents but not for black or Hispanic adolescents (SOR: **B**, cross-sectional survey).

A 2011 meta-analysis of 17 cross-sectional and longitudinal studies involving 182,836 children and adolescents examined the effects of family meal frequency on nutritional status by measuring body mass index (BMI), food consumption, and eating patterns.[1] Of the studies included, 12 were conducted in the United States, and 8 examined family meals in relation to weight status.

Children who ate 3 or more shared family meals per week were less likely to be overweight compared with children who had fewer than 3 shared meals (8 studies, n=44,016; odds ratio [OR] 0.88; 95% CI, 0.81–0.97). Patient ages in the included studies ranged from 4 to 17 years, but age was not found to moderate the effect of shared family meals on weight.[1]

A 2015 longitudinal cohort study surveyed more than 2,000 adolescents at ages 12 to 17 years and again 10 years later about their frequency of family meals and their weight to determine if family meal frequency during the adolescent years affected adult obesity.[2] BMI was calculated based on reported height and weight.

Family meal frequency of 1 to 2 per week during adolescence was associated with reduced odds of overweight and obesity 10 years later versus no history of family meals during adolescence (OR 0.55; 95% CI, 0.38–0.79). Family meal frequencies of 3 to 4 per week compared with none at all (OR 0.60; 95% CI, 0.42–0.85) and 5 or more compared with none at all (OR 0.63; 95% CI, 0.46–0.87) also resulted in decreased odds of being obese or overweight 10 years later.[2]

A 2006 cross-sectional study analyzed data from a 1997 US national survey of more than 5,000 adolescents between 12 and 15 years old to assess the association between overweight status and the frequency of family meals.[3] The investigators calculated respondents' BMI based on reported height and weight and compared BMI with frequency of family dinners.

Non-Hispanic white adolescents who ate 3 to 4 family dinners per week had a decreased risk of being overweight compared with those who ate no family dinners per week (n=2,736; OR 0.54; 95% CI, 0.30–0.98). However, these findings were not replicated in black and Hispanic adolescents, for whom 3 to 4 family dinners per week did not decrease the odds of being overweight versus no family dinners per week (n=2,278; OR 1.1; 95% CI, 0.73–1.7). The authors postulated that racial and ethnic differences in the caloric content of food or differences in portion sizes of food typically consumed during family dinners may account for these differences.[3] 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 Navy Medical Department, the Navy at large, or the Department of Defense.

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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.

What is the effectiveness of the shingles vaccine for preventing shingles in older adults?

Bottom line

The zoster vaccine effectively prevents shingles in patients older than 60 years, with a number needed to treat (NNT) of about 60 to prevent 1 case of shingles over 3 years (SOR: **B**, systematic review including single RCT). A newly approved vaccine may be more effective than the current vaccine, with a NNT of 33 (SOR: **B**, based on a single RCT). All adults 60 years and older should be routinely offered the herpes zoster vaccine (SOR: **C**, evidence-based expert opinion).

Evidence summary

A systematic review analyzed 13 RCTs (N=69,916) that examined the effectiveness of the herpes zoster vaccination in immunocompetent adults aged 60 years and older.[1] Only a large, multicenter US trial (n=38,546) compared the effectiveness of the currently available Food and Drug Administration-approved (FDA) single subcutaneous dose live-attenuated herpes zoster vaccine with placebo for the prevention of herpes zoster. Participants in this double-blinded study had a median age of 69 years (59% men, 95% white) and had a history of varicella or had lived in the continental United States for at least 30 years. The primary outcome was the incidence of herpes zoster confirmed by polymerase-chain reaction (PCR) analysis and clinical physician diagnosis. The mean duration of surveillance was 3.1 years (range 1 day to 5 years).

The incidence of herpes zoster was 1.6% in the vaccine group compared with 3.3% in the placebo group (relative risk [RR] 0.50; 95% CI, 0.44–0.56; NNT=59). The systematic review identified 1 additional RCT (n=8,122) in patients 60 years old and older using a newer adjuvanted recombinant varicella zoster virus subunit vaccine (known during development as HZ/su). This trial demonstrated a statistically significant reduction in the incidence of herpes zoster in the vaccine group compared with placebo at 3.2 years follow-up (RR 0.04; 95% CI, 0.02–0.10; NNT=33). The reviewers assessed that both RCTs had overall low risk for bias, although the studies were industry funded.[1]

A 2016 phase 3, multicenter, observer-blinded RCT compared the effectiveness of the HZ/su shingles vaccine with placebo in 13,163 people older than 70 years (mean age 75.6 years).[2] Participants had no history of herpes zoster or previous zoster vaccination. Vaccine and placebo were administered as deltoid muscle injections at trial enrollment and repeated 2 months later.

During a mean follow-up of 3.7 years, herpes zoster occurred in 0.4% of HZ/su recipients and in 3.4% of placebo recipients, yielding a vaccine efficiency rate of 89.8% (95% CI, 84–94; NNT=33). This vaccine was approved by the FDA for use in the United States on October 20, 2017.[2]

The Advisory Committee on Immunization Practices evidence-based recommendations advise the herpes zoster vaccine be recommended routinely for adults aged 60 years and older.[3] EBP

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Does UV light improve acne?

EVIDENCE-BASED ANSWER

Moderate-to-severe facial inflammatory papular acne vulgaris improves slightly with narrow-band UVB treatment combined with oral azithromycin compared with oral azithromycin alone (SOR: **B**, small, unblinded RCT). The use of UVA or B light therapy alone or in combination with other medications may have no benefit (SOR: **C**, single low-quality, nonrandomized trial).

A 2014 randomized, open-label clinical trial compared oral azithromycin, 500 mg 3 times a week (control group) versus the same dose of azithromycin plus narrow-band UVB light therapy (intervention group) (5 minutes to each of 4 zones of the face twice a week) in 104 patients with moderate to severe inflammatory acne vulgaris of the face.[1] The patients were evaluated by clinical assessment of photographic records after 2 and 4 weeks of therapy. Total lesion count (papules, pustules, cysts or nodules) was measured as well as the specific number of lesions in each of 4 zones (forehead, central face, left face and right face). Ten subjects withdrew from the study (most for personal reasons, but 1 in the UVB group due to erythema).

The intervention group had a significant reduction in the number of inflammatory papules compared with the control group (89% vs 70% improvement; *P*=.002). No difference was noted between the groups in pustules, cysts, or nodules. The forehead zone improved more than the other zones in group 2 (78% decrease in inflammatory papules vs 58%; *P*=.02). Subject satisfaction with treatment was higher in the intervention group, but no scores were reported.[1]

A 1978 nonrandomized "preliminary" study compared a variety of phototherapy treatment options for acne (UVA, UVB, UVA+UVB, UVA+demeclocycline HCl, UVA+crude coal tar, and UVA+psoralen).[2] A total of 126 patients with moderately severe papulopustular acne were studied in unequal groups (of 11–27 subjects each). Method of assignment of the patients to the various groups was not described, and the amounts of UV exposure were not consistent between groups. Total lesion counts were assessed at baseline and after 8 weeks of treatment. Improvement was rated as excellent (75%–100%), good (50%–74%), fair (26%–49%), poor (0%–25%), or worse with treatment.

The group receiving demeclocycline and UVA improved the most (40% of patients with either good or excellent improvement), but 12% were worse due to phototoxic reactions. The authors suggested the addition of UVA did nothing more than the demeclocycline alone would have been expected to do. The UVB group showed good or fair improvement in 63% of patients and 11% were worse. The UVA group had either good or fair improvement in 33% and 40% were worse. The authors concluded that the UV exposure did not add benefit over "usual" topical regimens (benzoyl peroxide and tretinoin).[2]

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Are amphetamines helpful for adults with ADHD?

EVIDENCE-BASED ANSWER

Amphetamine medications lead to large improvements in symptom severity in adults with attention deficit hyperactivity disorder (ADHD) over the short term; however, patients given amphetamines are more likely to stop treatment due to adverse events. Long-term efficacy has not been established (SOR: **A**, meta-analyses of RCTs).

A systematic review of 7 RCTs with 1,091 participants evaluated treatment with amphetamines for adults with ADHD.[1] The included studies examined the efficacy of lisdexamfetamine, dextroamphetamine, and mixed amphetamine salts. The comparators were either placebo or active treatment with guanfacine, modafinil, or paroxetine. Severity of ADHD symptoms was assessed by various standardized instruments in the included trials, so results were reported as standardized mean differences (SMD). Secondary outcomes included retention in treatment and withdrawal due to adverse events. Study duration was 2 to 20 weeks (median 7 weeks).

Treatment with amphetamines moderately improved severity of ADHD symptoms compared with placebo (6 studies, n=1,045; SMD –0.7; 95% CI, –0.9 to –0.6), but not retention in treatment (6 studies, n=1,072; risk ratio [RR] 1.1; 95% CI, 1.0–1.2). Amphetamine treatment was associated with an increased risk of withdrawal due to adverse events compared with placebo (4 studies, n=998; RR 3.0; 95% CI, 1.5–6.1).[1]

The data were limited by short follow-up, and no study was free from bias as the subjective effects of amphetamines likely would have revealed treatment assignment. Additionally, the external validity of the included studies was in question as patients with comorbid psychiatric disorders or substance abuse—common among persons with ADHD—were excluded.[1]

In 2014, a meta-regression analysis estimated the treatment effect of lisdexamfetamine in adults with ADHD.[2] The researchers derived the estimated effect using indirect comparisons of results obtained from 23 double-blind RCTs (N=6,326) of US adults, adolescents, and children with ADHD treated with lisdexamfetamine, as well as European and US adults, adolescents, and children with ADHD treated with atomoxetine or methylphenidate. For each comparison, the researchers calculated an effect size (similar to SMD) to report the average improvement in the various symptom scoring instruments used in the studies, including the ADHD-Rating Scale IV, Conners' Adult ADHD Rating Scale, and the Adult ADHD Investigator Rating Scale.

The analysis estimated a large treatment effect of lisdexamfetamine of 1.1 (95% CI, 0.8–1.4) for European adults and 0.8 (95% CI, 0.6–1.1) for US adults.[2]

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Are phosphodiesterase inhibitors effective and safe for men with diabetes and erectile dysfunction?

EVIDENCE-BASED ANSWER

Yes. As-needed use of sildenafil, tadalafil, and vardenafil lead to large improvements in erectile function in men with diabetes. Tadalafil taken daily results in nearly 20% more men able to complete intercourse, but only marginal clinical benefit in overall erectile function compared with placebo. Adverse events occur up to twice as often with phosphodiesterase type 5 (PDE-5) inhibitors than placebo, but are minor such as headache and dyspepsia (SOR: **A**, meta-analyses of RCTs). Vardenafil taken daily improves global erectile function scores, with mean scores at the level considered to be normal erectile function (SOR: **B**, single RCT).

A 2015 meta-analysis of 14 double-blind RCTs and 3 open randomized trials compared efficacy and safety of PDE-5 inhibitor therapy with placebo for treatment of erectile

dysfunction in 5,230 men with diabetes (age range 46–59 years) over 10 days to 16 weeks.[1] The studies used different outcome measures, so "improved erectile function" was defined as a positive response to any global assessment of erectile function such as the Global Assessment Questionnaire, asking if erections have improved, or asking the Sexual Encounter Profile question 2—if able to insert penis in partner's vagina.

In pooled analysis (number of pooled trials not reported), all PDE-5 inhibitors improved erectile function, with the largest standardized mean difference (SMD) for sildenafil 25 to 100 mg (n=1,041; SMD 1.2; 95% CI, 1.0–1.3; number needed to treat [NNT]=3), then tadalafil 2.5 to 20 mg (n=1,584; SMD 0.91; 95% CI, 0.84–0.98; NNT=3), and then vardenafil 5 to 20 mg (n=1,748; SMD 0.68; 95% CI, 0.63–0.73; NNT=5). The dosing for vardenafil was as needed in all included studies, whereas the dosing for sildenafil and tadalafil varied from as needed to once daily. Most common adverse events included headache, dyspepsia, hot flushes, rhinitis, and nasal congestion, with a median adverse event ratio of 1.9 for treatment to placebo.[1]

A 2014 pooled analysis of 6 RCTs, totaling 1,913 patients, included a subgroup analysis of 543 men with diabetes (mean age 58 years) comparing the efficacy and safety of tadalafil 2.5 and 5 mg daily with placebo for treatment of erectile dysfunction over 12 weeks.[2] One RCT of 298 men with diabetes was included in both this analysis and the 2015 analysis discussed above. The validated International Index of Erectile Function (IIEF-EF) questionnaire was used to measure erectile function (scored 1–30, higher scores indicating improved erectile function, and normal defined as ≥26). Changes in IIEF-EF scores of 4 or more were interpreted as clinically relevant. The number of trials pooled for each outcome was not reported.

Patients receiving 2.5 mg had a change of 4.0 points over placebo (n=143; 95% CI, 2.5–5.5), and patients receiving 5 mg had a mean change of 3.6 points (n=215; 95% CI, 2.3–5.0). Using the percent of "yes" responses to Sexual Encounter Profile question 3: "Did your erection last long enough for you to have successful intercourse?", patients receiving 2.5 mg were 19% more likely to answer "yes" than patients using placebo (n=140; 95% CI, 12–26), and patients receiving 5 mg had 17% more "yes" responses (n=216; 95% CI, 11–24). Tadalafil 2.5 and 5 mg were more likely to normalize erectile function (IIEF-EF score ≥26) than placebo (n=134; OR 1.9, 95% CI, 1.1–3.4 and n=208; OR 1.9, 95% CI, 1.1–3.2, respectively). The most common adverse events seen in the placebo, 2.5 mg, and 5 mg groups were headache (4.5%, 2.5%, 6.9%, respectively) and dyspepsia (1.5%, 2.3%, 4% respectively).[2]

A 2016 RCT evaluated 24 weeks of vardenafil 10 mg twice daily versus placebo in 45 patients with erectile dysfunction and type 2 diabetes (mean age 56 years).[3] The mean IIEF-EF scores after 12 weeks were significantly higher in the vardenafil group than the placebo group (26 vs 18; $P<.001$). Blood counts, liver function, and renal function were reported as normal throughout the study, but data were not published.

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In patients with substance abuse disorder, is Suboxone® more effective than methadone for treatment of opioid dependence?

EVIDENCE-BASED ANSWER

Both treatments are likely about the same in efficacy (SOR: **C**, conflicting blinded and unblinded clinical trials). Suboxone-prescribing sites are more widely available.

A 2008 randomized, double-blind, double-dummy trial compared fixed low- and high-dose Suboxone (buprenorphine and naloxone 8/2 vs 16/4 mg) to fixed low- and high-dose methadone (45 and 90 mg) in opioid-dependent patients (N=268).[1] Mean age was 38 years and 72% were male.

The percentage of opioid-free urine samples over 17 weeks remained about the same (only reported graphically, estimated to be 10%–20%) and did not differ by medication

type (*P*=.81). Medication compliance, measured by the number of doses directly observed in clinic (home dosing not allowed) did not differ significantly between treatments, ranging from 38 to 49 doses (*P*=.41). Average retention in treatment with either medication was about 12 weeks, but no difference was noted between low- or high-dose Suboxone versus methadone.[1]

A 2014 randomized, open-label, multicenter phase 4 trial investigated liver function in patients randomized to methadone or Suboxone for 24 weeks (N=1,267).[2] Mean age was 37 years and 78% were male. Methadone and Suboxone sublingual tablets were dispensed with a 3-day induction period, with a mean daily dose of methadone 93.2 mg and of Suboxone 22/5.5 mg.

In a secondary analysis, patients taking methadone were more likely than patients taking Suboxone to complete the trial (74% vs 46%; *P*<.01). Patients taking lower medication doses (<60 mg methadone or <16/4 mg Suboxone) were more likely to drop out than patients on higher doses (>60 mg methadone or 32/8 mg Suboxone; hazard ratio 3.1; 95% CI, 2.2–4.4). Completion rates increased to 80% for methadone doses of 60 mg or more and 60% for Suboxone doses of 30/7.5 mg or more. The mean number of days in treatment was greater with Suboxone than methadone (104 vs 141 days; *P*<.01). Within the first 30 days of treatment, significantly more patients in the Suboxone group dropped out than the methadone group (25% vs 8.3%; *P*<0.01). However, positive urine heroin results occurred significantly less often among participants taking Suboxone versus methadone (odds ratio [OR] 0.63; 95% CI, 0.52–0.76).[2]

A 2009 randomized, open-label trial of male prison inmates with opioid use disorder investigated treatment completion using methadone or Suboxone while imprisoned and subsequent reporting to the assigned treatment after release (N=133, trial duration 10–90 days).[3] Mean participant age was 39 years. Initial Suboxone dose was 8/2 mg on the first day and titrated to a maximum of 32/8 mg. Initial methadone dose was 30 mg daily and titrated to a maximum of 70 mg. Median daily doses at release from prison were 12/3 mg Suboxone and 30 mg methadone.

Significantly more patients taking Suboxone completed treatment (82% vs 75%; *P*<.05). Further, patients taking Suboxone reported for their postrelease treatment in the community significantly more often than patients taking methadone (48% vs 14%; *P*<.001). However, patients taking Suboxone were in treatment for significantly less time than patients taking methadone (23 vs 32 days, respectively; *P*<.05). No postrelease differences were found for relapse to illicit opioid use between the 2 groups at the 3-month follow-up (14% Suboxone vs 14% methadone; *P*>.05).[3]

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Are self-swabs as effective for screening for vaginal STIs as swabs collected during a speculum exam?

EVIDENCE-BASED ANSWER

Yes. Self-obtained vaginal swabs are nearly equivalent to clinician-collected cervical specimens in the diagnosis of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (SOR: **A**, based on a meta-analysis). Self-obtained vaginal swabs are the preferred method of collection for detection of chlamydia and gonorrhea (SOR: **C**, expert opinion).

A 2015 meta-analysis of 21 studies (N=18,956) compared the use of self-collected versus clinician-collected specimens in the detection of chlamydia and gonorrhea using a polymerase chain reaction (PCR) test.[1] The meta-analysis included randomized and nonrandomized controlled trials as well as cross-sectional observational studies. Twenty of these composite studies evaluated chlamydia (n=12,916) and 7 studies evaluated gonorrhea (n=6,040) with 6 studies evaluating both infections. The gold standard was considered to be cervical specimens obtained by a clinician during a speculum examination. The ages of participants, when

reported, varied from 14 to 56 years. The studies also varied on whether or not the patients were symptomatic prior to cervical swab collection.

Comparing self-collected vaginal swabs with clinician-collected cervical swabs, the chlamydia cross-sectional observational studies (4 trials, n=994; prevalence 6.8%–12.6%) resulted in a pooled sensitivity of 0.89 (95% CI, 0.82–0.94) and a specificity of 0.98 (95% CI, 0.97–0.99). For gonorrhea, the cross-sectional observational study comparing self-collected vaginal swabs versus clinician-collected cervical swabs (1 trial, n=309; prevalence 14.2%) showed a sensitivity of 0.98 (95% CI, 0.88–1.00) and a specificity of 0.97 (95% CI, 0.94–0.99).[1]

The Centers for Disease Control and Prevention (CDC), in their 2014 *Morbidity and Mortality Weekly Report*, advocated for the use of self-collected vaginal swabs for the detection of both chlamydia and gonorrhea.[2] After performing a Medline database review, the CDC determined that the sensitivity and specificity of self-swabs were equivalent to clinician-obtained cervical specimens and therefore adequate for the detection of these 2 sexually transmitted infections.

Among all collection types (cervical, urinary, and vaginal), the CDC recommended vaginal swabs as the preferred form of collection for detection of genital chlamydia and gonorrhea (no strength of recommendation provided).[2]

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Does hypertonic saline infusion with furosemide improve outcomes for patients with acute CHF exacerbation?

EVIDENCE-BASED ANSWER

Perhaps. In patients treated for acute congestive heart failure (CHF), hypertonic saline infusion with furosemide decreases all-cause mortality by 44%, hospital readmission rates by 50%, and length of stay by about 3 days compared with furosemide alone (SOR: **B**, meta-analysis of lower quality RCTs and small RCT). However, patients in these studies were not consistently on current guideline-directed medical therapy.

A 2014 systematic review and meta-analysis of 10 single- and double-blinded RCTs (N=2,845) compared outcomes between furosemide and hypertonic saline solution versus furosemide alone in patients with acute CHF.[1] Furosemide was administered intravenously (IV) and given as a once-daily bolus (40–1,000 mg in 5 studies), twice-daily bolus (250–1,000 mg in 4 studies), or an unspecified amount titrated at the physician's discretion based on clinical response (1 study). Hypertonic saline was administered IV as follows: 150 to 500 mL of 1.7% to 7.5% hypertonic saline daily (4 studies), 150 mL of 1.4% to 4.6% hypertonic saline daily based on serum sodium (1 study), or 15 mL/kg daily (5 studies). Outcomes compared all-cause mortality, heart failure hospital readmission, length of stay, weight loss, and changes in serum creatinine concentration.

Furosemide and hypertonic saline compared with furosemide alone improved all-cause mortality (5 studies, n=2,064; risk ratio [RR] 0.56; 95% CI, 0.41–0.76), reduced hospital readmissions (4 studies, n=2,032; RR 0.50; 95% CI, 0.33–0.76), reduced length of stay (7 studies, n=2,719; –3.1 days; 95% CI, –4.2 to –2.0), increased mean weight loss (8 studies, n=2,651; –9.8 vs –7.7 kg; $P<.05$), and improved serum creatinine concentration (8 studies, n=2,651; decrease of 0.20 mg/dL vs increase of 0.30 mg/dL; $P<.05$). No studies reported major adverse effects with hypertonic saline that required cessation of participation. The authors noted that many of these RCTs were conducted in the 1990s when patients were less likely to be treated with beta-blockers or angiotensin-converting enzyme inhibitor therapy (no data reported).[1]

CONTINUED

A 2015 randomized single-blinded study (N=43) compared 3 diuretic regimens for acute decompensated CHF.[2] The patients were an average age of 69 years and mostly men; they had pro-BNP levels of more than 300 pg/mL and mean left ventricular ejection fraction of 42%, and were hospitalized for acute decompensated CHF. Patients were randomized into 3 groups: furosemide 160 mg continuous infusion for 16 hours daily, furosemide 80 mg bolus injections twice daily, or furosemide 160 mg plus 1.95% hypertonic saline as a 30-minute infusion once daily. Outcomes included weight loss, hospital length of stay, and change in baseline serum creatinine concentration after 48 hours of treatment and after compensated state was reached.

No difference was noted in weight loss among the hypertonic saline, continuous furosemide infusion, and furosemide bolus groups (losses of 5.7 kg vs 4.6 kg vs 4.1 kg; *P*=.66). The hypertonic saline group compared with the continuous infusion and bolus groups had shorter hospital stay (3.7 days vs 6.6 days and 7.9 days; *P*<.01). No between-group differences were noted for changes in serum creatinine concentration. The bolus group had significantly lower beta-blocker use than the other 2 groups (bolus group 29% vs infusion group 60% and hypertonic saline group 79%; *P*=.02).[2]

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

What are the predictors of postconcussion syndrome after head injury in children and young adults?

EVIDENCE-BASED ANSWER

In children evaluated for head injury, predictors of future postconsussion syndrome include older age, headache, delayed onset of symptoms, previous concussion, history of mood disorder, family history of migraine or mental illness, and markers of severity of injury such as need for analgesics, performance of head computed tomography (CT), and hospital admission (SOR: **B**, cohort and case-control studies). In college-age athletes, postconcussion syndrome is predicted by previous concussion and symptoms such as amnesia, poor concentration, photophobia, and insomnia at presentation (SOR: **B**, case-control study).

A 2013 cohort study evaluated predictors of postconcussion syndrome among 547 pediatric patients 5 to 18 years of age who presented to emergency departments (ED) with mild traumatic brain injury (TBI), which is synonymous with concussion.[1] Mild TBI was defined as a blow to the head or acceleration-deceleration movement of the head resulting in 1 or more of the following signs or symptoms: loss of consciousness (LOC) of less than 30 minutes, amnesia of less than 24 hours or any alteration in mental state, or a Glasgow Coma Scale score of 13 or more measured at least 30 minutes after injury.

Postconcussion syndrome was defined as 3 or more concussion symptoms (headaches, dizziness, nausea, noise sensitivity, sleep disturbance, fatigue, irritability, depression, frustration, poor memory, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision, and restlessness) persisting for longer than 3 months with a severity score of 2 or more (range 0–4) on the Rivermead Post Concussion Symptom Questionnaire (RPQ).[1]

Of the 406 patients with 3 months of follow-up, 119 had postconcussion syndrome. Postconcussion syndrome was associated with the following factors at the time of concussion: age 11 to 18 versus 5 to 10 years (relative risk [RR] 1.8; 95% CI, 1.1–2.9), headache (RR 2.1; 95% CI, 1.3–3.2), performance of head CT (RR 1.4; 95% CI, 1.1–2.0), analgesics

administered in the ED (RR 1.5; 95% CI, 1.1–2.1), and hospital admission (RR 1.9; 95% CI, 1.3–2.6). Male sex decreased the risk of postconcussion syndrome (RR 0.71; 95% CI, 0.53–0.96). At 3 months follow-up, postconcussion syndrome was associated with analgesics administered at home (RR 1.8; 95% CI, 1.3–2.6), more than 2 days of school missed (RR 2.0; 95% CI, 1.5–2.6), self-interview versus parent interview (RR 1.5; 95% CI, 1.1–2.0), and intent to sue (RR 2.3; 95% CI, 1.7–3.0). Limitations of this study included phone interviews at 3 months rather than in-person examination and the RPQ was not validated for the definition of postconcussion syndrome in this study.[1]

A 2015 case-control study assessed predictors of postconcussion syndrome among 120 athletes 9 to 18 years of age with sports-related concussion from the Vanderbilt Sports Concussion Center database between 2011 and 2013.[2] Concussion diagnoses were made by athletic trainers or team physicians on the field or sideline at the time of injury if the athletes had typical signs and symptoms of concussion. Case patients had concussion symptoms persisting 3 months or more and control patients had concussion symptoms that lasted less than 3 weeks.

Postconcussion syndrome was associated with the following factors at the time of injury: previous concussion (odds ratio [OR] 1.8; 95% CI, 1.1–2.8), delayed symptoms or symptom onset 3 or more hours during the peri-injury period (OR 21; 95% CI, 3–130), history of mood disorder (OR 18; 95% CI, 3–110), and family history of migraine, mood disorder, or psychiatric history (OR 3; 95% CI, 1–9).[2]

A 2016 case-control study evaluated predictors of postconcussion syndrome based on data extracted from the National Collegiate Athletic Association Injury Surveillance program database of 1,866 collegiate student athletes with sports-related concussions.[3] Diagnosis was made by athletic trainers or physicians, but a predetermined definition of concussion was not standard. The postconcussion syndrome group had 1 or more typical concussive symptoms persisting for more than 4 weeks. The control group had resolution of symptoms within 2 weeks. Among the 1,507 concussed athletes who met inclusion criteria, 112 (7.4%) had postconcussion syndrome.

On multivariate analysis, postconcussion syndrome was associated with the following factors present at the time of concussion: recurrent concussion (OR 2.1; 95% CI, 1.3–3.4), retrograde amnesia (OR 2.8; 95% CI, 1.3–5.6), difficulty concentrating (OR 2.4; 95% CI, 1.2–4.5), sensitivity to light (OR 2.0; 95% CI, 1.1–3.6), and insomnia (OR 2.2; 95% CI, 1.3–3.7).[3]

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Does smoking cannabis help with chronic neuropathic pain?

EVIDENCE-BASED ANSWER

Yes. Cannabis decreases refractory neuropathic pain in conjunction with analgesics when smoked over 3 hours for 5 days, with no difference between 3.5% and 7% tetrahydrocannabinol (THC) concentrations (SOR: **C**, systematic review of small RCTs).

A systematic review of 6 RCTs (N=226) examined the efficacy of cannabis for chronic noncancer pain.[1] Five of the trials (n=189) were rated as high quality (with Jadad scale scores of >2) and assessed the use of low-dose THC as an adjunct to patients' existing analgesics for treatment of neuropathic pain.

All the studies reported a statistically significant reduction in pain in the cannabis group compared with placebo. However, a clinically meaningful reduction in pain (a decrease of 2 points on a 0–10 numerical pain rating or a 30% improvement in pain intensity) was reported in 3 of the 5 studies, with 46%, 52%, and 61% of cannabis users reporting benefit versus 18%, 25%, and 26% of the placebo group, respectively. Two of the largest trials with clinically meaningful reduction in pain will be discussed below in detail.[1]

A double-blind, placebo-controlled, crossover RCT evaluated the analgesic efficacy of smoked cannabis for

neuropathic pain in adults (N=38).[2] Patients completed 3 treatment sessions of 6 hours each. During these sessions, patients were given 3.5% THC, 7% THC, or placebo (0% THC). Patients inhaled 2 puffs at hour 1, 3 puffs at hour 2, and 4 puffs at hour 3, for a total of 9 cumulative puffs. Participants completed questionnaires before, after, and between each cannabis administration. Pain intensity was measured on a 100-mm visual analog scale (VAS; 100=worst possible pain).

Both potencies produced significant pain reduction in VAS per minute compared with placebo: for 3.5% THC the mean difference was –0.0036 mm/min (95% CI –0.0069 to –0.003), and for 7% THC the mean difference was –0.0035 mm/min (95% CI, –0.0068 to –0.0002). No difference was noted between 3.5% and 7% THC.[2]

A double-blind RCT compared the effect of smoked cannabis with that of placebo cigarettes for treating adults with painful HIV-associated sensory neuropathy (N=50).[3] Patients had an average pain score of at least 30 on the 100-mm VAS (100=worst pain imaginable) before the trial and were on a stable medication regimen. Patients were randomly assigned to either the placebo cigarette (0% THC) or 3.56% THC group. The study consisted of 4 phases: a 7-day outpatient pre-intervention phase, a 2-day lead-in phase, a 5-day inpatient phase with patients smoking 1 cigarette 3 times a day, and a 7-day postintervention phase with daily recorded pain scores. Patients kept a daily pain diary using the VAS throughout the study period.

From baseline to end of treatment, daily pain was reduced by 34% (median reduction) in the cannabis group (interquartile range [IQR] –71 to –16) versus a 17% reduction (IQR –29 to 8) in the placebo group (mean difference 18%; *P*=.03). In the cannabis group, 52% reported more than a 30% reduction in pain versus 24% in the placebo group (*P*=.04).[3]

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Can vitamin D supplementation decrease risk of statin-induced rhabdomyolysis in patients receiving statin therapy?

EVIDENCE-BASED ANSWER

Perhaps. In patients with a history of statin-induced myalgia or myopathy and documented low vitamin D levels, vitamin D supplementation allows more than 88% of patients to tolerate statin therapy with the same or an alternate statin (SOR: **B**, cohort studies).

A 2015 meta-analysis of 7 observational and crossover studies (N=2,420) evaluated the role of serum vitamin D levels in statin-induced myalgia in adults without comorbidities.[1] Vitamin D levels were significantly lower in statin-treated patients with myalgia symptoms than patients without such symptoms (weighted mean difference [WMD] –9.4 ng/mL; 95% CI, –10 to –8.6). Weaknesses in this study included heterogeneity of included studies, no placebo control, lack of blinding, and subjective outcome.[1]

In 2015, a prospective cohort study (N=146) evaluated vitamin D supplementation in vitamin D–deficient patients in whom 2 or more statins had failed due to myopathy.[2] Myopathy was defined as muscle pain or weakness with or without elevated CPK but no rhabdomyolysis. Men and women with a mean age of 59 years and vitamin D levels of less than 32 ng/mL were started on vitamin D supplementation (50,000–100,000 IU/week), rechallenged with statin therapy (rosuvastatin 10–20 mg/d), and followed for up to 24 months with 3 symptom surveys at 6, 12, and 24 months. Only 64 of the 146 patients completed all 3 surveys.

Of these 64 patients, 92% had normalized vitamin D levels (˜56 ng/mL). In the surveys completed at 6, 12, and 24 months, almost all patients were able to tolerate statin therapy (88%, 91%, and 95%, respectively). Weaknesses of this study included no randomization, no placebo control, challenge with a different statin, subjective outcome, and high loss to follow-up.[2]

In 2017, a retrospective cohort study evaluated vitamin D supplementation in veterans (N=27) with hyperlipidemia, history of statin-induced myalgia, and vitamin D deficiency (<30 ng/mL).[3] Patients received vitamin D supplementation (800–1,000 IU daily for patients with levels of 20–30 ng/mL,

and an additional 50,000 IU/week for patients with levels <20 ng/mL) for 12 months and restarted on a statin (atorvastatin, pravastatin, rosuvastatin).

At 1 year, all participants were able to tolerate statin therapy, with 41% receiving the same previously untolerated statin, 55% at the same dose. Weaknesses of this study included no randomization, no placebo control, a small number of participants, and subjective outcome.[3]

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

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Do antibiotics provide symptom relief for mastitis from breastfeeding?

EVIDENCE-BASED ANSWER

For breastfeeding women with mastitis, antibiotics combined with breast emptying may lead to faster and more complete resolution of symptoms than breast emptying alone or no treatment (SOR: **C**, low-quality RCT). The choice of antibiotics within the beta-lactam class does not appear to change time to resolution (SOR: **C**, low quality RCT).

A 2013 systematic review (2 RCTs, N=190) examined the effectiveness of antibiotic therapy for relieving symptoms of mastitis in breastfeeding women.[1] Lactating women with clinical mastitis (with or without supporting laboratory evidence) received antibiotic therapy, placebo, or nonpharmacologic therapies for treatment of mastitis. Exclusion criteria included lactating women with breast engorgement without clinical mastitis or with breast abscesses. The primary outcomes were symptom improvement, continued breastfeeding, and resolution of infection. Only 2 trials met inclusion criteria but results could not be pooled due to different outcome measures and different comparison groups, so the trials are summarized separately.

The authors of the systematic review thought evidence was insufficient to evaluate antibiotics for mastitis due to low-quality RCTs with concern for selection, performance, detection, attrition, and reporting bias.[1]

The first trial was a 1984 RCT (N=165) evaluating antibiotic treatment with breast emptying versus no treatment or breast emptying only.[2] Diagnosis of mastitis was based on clinical symptoms (presence of persistent tenderness, swelling, erythema, warmth, and decreased milk production), elevated leukocyte count, and positive cultures. Control groups received either no treatment or "breast emptying," described as nursing the baby every 6 hours followed by hand or mechanical milk extraction. The antibiotic group performed breast emptying and received parenteral penicillin (500,000 IU TID for 6 days), ampicillin (500 mg QID for 6 days), or erythromycin (500 mg BID for 6 days) based on culture susceptibility tests.

The mean duration of mastitis symptoms was significantly shorter (2.1 days) in the antibiotics with breast-emptying group versus 4.2 days in the breast-emptying group and 6.7 days in the no-treatment group ($P<.001$ for both comparisons). Women receiving antibiotics with breast emptying were more likely to have treatment success defined as resolution of inflammatory symptoms and resumption of normal lactation within 14 days of beginning treatment compared with breast emptying alone (risk ratio [RR] 1.9; 95% CI, 1.5–2.5) or no treatment (RR 6.6; 95% CI, 3.5–13).[2]

The second trial was an investigator-blinded RCT from 1996 examining 25 lactating women with sporadic, acute puerperal mastitis comparing treatment with 2 different antibiotics.[3] Women were at least 18 years old and had temperatures of at least 37.6°C, tenderness on palpation of the breast, and segmental erythema. Patients with documented allergies to the antibiotics or who were prescribed antibiotics in the last 30 days were excluded. Oral amoxicillin 500 mg every 8 hours for 7 days was compared with cephradine (not available in the United States) 500 mg every 8 hours for 7 days. Both groups were instructed to continue breastfeeding and use warm compresses every 4 to 6 hours.

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No significant difference was noted between the treatment groups in mean days to resolution of fever, erythema, and tenderness (amoxicillin 4.2 days vs cephradine 3.8 days) Similarly, no difference was noted in clinician-determined resolution of symptoms at 7 days (RR 0.85; 95% CI, 0.65–1.1).[3]

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Does topical nitroglycerin improve pain in adult patients with tendinopathy of the lower extremity?

EVIDENCE-BASED ANSWER

For Achilles tendinopathy, topical glyceryl trinitrate (GTN) results in small improvements in multiple measures over 12 weeks. At 3 years about 20% more patients are asymptomatic (SOR: **C**, small RCT with long-term follow-up). For chronic patellar tendinopathy, GTN has no effect on pain (SOR: **C**, small RCT).

A 2004 randomized, double-blind, placebo-controlled trial (N=58) compared 24 weeks of continuous nitroglycerin patches versus placebo patches for chronic noninsertional Achilles tendinopathy.[1] The treatment group received 1.25 mg topical GTN every 24 hours via quartered Nitro-Dur® patches. The placebo group received a similar, quartered inert Nitro-Dur demonstration patch. Both groups were instructed to wear 1 to 1.5 cm heel-raise wedges and complete home physical therapy (rest, stretching, and eccentric exercises).

Using a 5-point scale (0 indicating no pain and 4 indicating very severe), the GTN group had lower mean pain scores with activity compared with placebo at 12 weeks (0.9 vs 1.6 points; *P*=.02) and 24 weeks (0.4 vs 1.0 point; *P*=.03). At 12 weeks, the GTN group also had less night pain (0.2 vs 0.7 points; *P*=.04) and less tenderness (0.9 vs 1.6 points; *P*=.02). No difference was seen in night pain and tenderness at 24 weeks.[1]

In 2007, a 3-year follow-up of the study above compared the long-term effect of GTN treatment on chronic noninsertional Achilles tendinopathy.[2] Fifty-two of the original 58 participants (90%) completing 24 weeks of GTN or placebo were available for follow-up.

Using the same 5-point scale, the GTN group had less Achilles tendon tenderness than placebo (results only reported graphically but difference appears to be about 0.5 points; *P*=.03). In addition, on the Victorian Institute of Sports Assessment-Achilles questionnaire (VISA-A; 0=no activity/maximum pain, 100=maximum activity/no pain) the GTN group had scores about 5 points better than placebo (*P*=.04). Significantly more patients were asymptomatic (VISA-A scores of 100) in the treatment group than the placebo group (88% vs 67%; *P*=.03). No differences were noted in pain with activity and night pain.[2]

A 2013 randomized, double-blind, placebo-controlled trial (N=33) compared the effect of 12 weeks of continuous GTN treatment on chronic patellar tendinopathy.[3] The treatment group (n=16) received nitroglycerin patches that delivered 5 mg GTN every 24 hours. The placebo group (n=17) received blister-plasters. Both groups were told to complete home physical therapy (eccentric and concentric components) and advised to avoid weight-bearing sporting activities for 4 weeks, then gradually return to usual activities. They were questioned at 6, 12, and 24 weeks. Primary outcomes were evaluated using the Victorian Institute of Sports Assessment-Patella questionnaire (VISA-P; 0=no activity/maximum pain, 100=maximum activity/no pain).

At 24 weeks, scores improved from baseline values in the treatment group (from 63 to 75) and in the placebo group (from 68 to 81). The change from baseline in each group was significant (*P*<.01), but not the between-group differences (*P*=.80). Secondary outcome was pain measured using an 11-point visual analog scale (0=worst pain and 10=no pain), and after 24 weeks, pain scores improved from baseline in the treatment group (from 4.1 to 6.6) and in the placebo group (from 5.8 to 7.8). Again, improvement within groups

was significant (*P*<.01), but not between groups (*P*=.38). The study was powered to detect a 13-point difference in the VISA-P.[3]

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How do you identify patients with nonalcoholic fatty liver disease who have progressed to nonalcoholic steatohepatitis?

EVIDENCE-BASED ANSWER

Ultrasound is useful for finding patients with high degrees of steatosis at risk for nonalcoholic steatohepatitis (NASH), but is less useful for finding nonalcoholic fatty liver disease (NAFLD) if steatosis involves less than 30% of the liver. Magnetic resonance imaging (MRI) performs better than ultrasound if steatosis is less than 25% but more than 10%. Alanine transaminase (ALT) levels are poor predictors of the presence of NASH (SOR: **C**, systematic review of RCTs and observational studies and meta-analysis of diagnostic cohort studies). After excluding other causes of liver disease, the NAFLD Fibrosis Score is useful for determining which patients may need a biopsy to evaluate for NASH (SOR: **C**, expert opinion).

A 2015 systematic review examined 14 RCTs, 19 cohort or case-controlled studies, 1 population-based study, 7 meta-analyses, 2 practice guidelines, and 43 other sources to identify patients (N not reported) with NAFLD who were at high risk for NASH and cirrhosis.[1]

Three studies (study type not reported) found 30% to 60% of biopsy-confirmed NASH cases had normal ALT levels and although the source was not cited, the review authors stated that the sensitivity and specificity of an elevated ALT level for diagnosing NASH was 45% and 85%, respectively (positive likelihood ratio [LR+] 3; negative likelihood ratio [LR–] 0.64).[1]

The authors also noted that, in general, patients who have hepatic steatosis and metabolic syndrome are at risk for developing NASH and are candidates for liver biopsy. However, noninvasive assessment such as ultrasound, computed tomography (CT), or MRI is considered the appropriate first step in determining the need for liver biopsy to diagnose suspected NASH in patients with hepatic steatosis. A prospective study of 73 consecutive patients found ultrasound had a sensitivity close to 100% and specificity of 90% (LR+ 10) for diagnosing steatosis when it involved more than 30% of the liver. However, with less than 30% involvement of the liver, ultrasound had a sensitivity of less than 43% and a specificity of 73% (LR+ 1.6; LR– 0.78). The review authors stated that CT did not improve sensitivity over ultrasound, but they did not provide actual data to support the statement. However, a cohort study showed MRI could detect steatosis involving just 5.56% of the liver with nearly 100% accuracy.[1]

A 2011 meta-analysis of 46 prospective and retrospective cohort studies (N=4,715) compared accuracy of ultrasound, CT, and MRI in detecting varying steatosis levels confirmed on biopsy.[2] Levels of steatosis ranged between 0% and 10% in group 1 to steatosis of more than 50% in group 4.

Using diagnostic odds ratio (DOR) to determine discriminatory test performance, MRI (DOR 5.2; 95% CI, 3.4–7.1) performed better than ultrasound (DOR 3.1; 95% CI, 2.1–4.1; *P*=.05 vs MRI) and CT (DOR 2.3; 95% CI, 1.7–2.9; *P*<.01 vs MRI) for steatosis between 10% and 25%. MRI, ultrasound, and CT were equivalent for steatosis less than 10% or more than 25%. Data analysis for group 4, who had steatosis of more than 50%, was only possible for the ultrasound group.[2]

A 2012 evidence- and consensus-based practice guideline on NAFLD and NASH diagnosis and management from the American Association for the Study of Liver Disease was compiled from formal review and analysis of current studies, but exact methodology was not included.[3] The guidelines stated that NAFLD should be diagnosed only after other etiologies of liver disease are excluded (strong recommendation; high-quality evidence) in the absence of excessive alcohol usage (defined as >21 drinks per week in men and >14 drinks per week in women), with confirmation on imaging or histology. No recommendation was made for a specific imaging modality.

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The guidelines further stated that liver biopsy should be selected judiciously when a patient is considered high risk for advancing NASH and fibrosis or when underlying competing causes of liver disease cannot be otherwise ruled out (strong recommendation, moderate-quality evidence). The NAFLD Fibrosis Score was noted as a clinically useful tool for identifying patients with NAFLD with a higher likelihood of having bridging fibrosis and/or cirrhosis (strong recommendation, moderate-quality evidence).[3]

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Does treatment with a statin improve erectile dysfunction symptoms?

EVIDENCE-BASED ANSWER

Yes. Among men with erectile dysfunction, treatment with a statin improves erectile dysfunction symptoms, and combining a statin with sildenafil results in greater improvements than sildenafil alone (SOR: **A**, meta-analyses of RCTs). Statins also improve erectile dysfunction–related quality of life in men with severe erectile dysfunction (SOR: **B**, single RCT).

A random-effects meta-analysis of 11 RCTs compared men with erectile dysfunction taking a statin (atorvastatin, simvastatin, or rosuvastatin; n=360) to men with erectile dysfunction taking placebo (7 studies, n=201) or no medication (4 studies, n=152).[1] Ages ranged from 49 to 63 years (mean 57 years). The duration of the trials varied from 1.5 to 6 months (mean duration 4.2 months). Outcome measurements included the validated International Index of Erectile Function (IIEF-5) scale, which rates the confidence in, adequacy and duration of, and satisfaction with erections on a 1 to 5 scale, with a maximum score of 25 indicating no dysfunction.

Use of statins was associated with an IIEF-5 score 3.4 points higher than control (11 trials, n=713; 95% CI, 1.7–5.0). The effect remained statistically significant after multiple sensitivity analyses, including analysis for publication bias and omitting each study sequentially. The studies were homogeneous, with *P* for heterogeneity equal to 0.72 and I^2=0.00.[1]

A systematic review and random-effects meta-analysis of 6 RCTs (N=462) evaluated the effect of statins on erectile dysfunction in men 56 to 63 years old.[2] Three trials were not included in the meta-analysis above and compared atorvastatin (40 or 80 mg) plus sildenafil 100 mg with placebo plus sildenafil 100 mg over 3 months.

Atorvastatin plus sildenafil increased IIEF-5 scores 3.7 points more than placebo plus sildenafil (3 trials, n=156; 95% CI, 2.3–6.0).[2]

A secondary analysis of a double-blind RCT evaluated the effect of simvastatin on male erectile dysfunction–specific quality-of-life scores (MED-QoL) in 173 eligible men.[3] The MED-QoL consists of 21 questions assessing the effects of erectile dysfunction on the patient's feelings of control, intimacy, and emotion, with scores ranging from 0 to 100 (higher scores indicating improved quality of life).

When given to men at least 40 years old with untreated erectile dysfunction (IIEF <22) and no other cardiovascular risk factors, simvastatin 40 mg daily for 6 months versus placebo led to larger improvements in MED-QoL scores (5% improvement vs 2% improvement; *P*=.04). Using a regression model, the mean total MED-QoL score in men with severe erectile dysfunction (IIEF <8) treated with a statin was 66.1 versus 58.3 with placebo (12% improvement vs 5% improvement; *P*<.001). The mean total revised scale score (MED-QoL-R) in men with mild/moderate erectile dysfunction treated with a statin (70.7) was similar to placebo (68.7).[3]

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Is topical vitamin E effective in promoting wound and scar healing?

EVIDENCE-BASED ANSWER

Probably not. Vitamin E may be effective for the management of surgical wounds in children, but not adults (SOR: **C**, systematic review of conflicting RCTs). Vitamin E may induce faster healing of digital ulcers in systemic sclerosis (SOR: **C**, single small RCT).

A 2016 systematic review found 6 RCTs (N=749) using topical vitamin E alone or in combination with other medications in treatment of scars.[1] The population sizes ranged from 15 to 428 patients; 5 trials included adults and 1 trial included children only. Three trials were double-blind, 2 were single-blind, and 1 was not blinded. The wounds were mostly surgical (5 studies); 1 study also included patients with burn scars, and another treated patients with keloids and hypertrophic scars. Each study assessed subjective scar appearance using photography or observer rating on a variety of different scales (Vancouver Scar Scale, Patient and Observer Scar Assessment Scale, Visual Analog Scale, and Scott-Huskisson Scale).

Of the 6 studies, 3 (n=211) showed no improvement in cosmetic appearance with vitamin E used as monotherapy. Two studies (n=110) showed benefit from using vitamin E in combination with silicone sheets; however, the degree of improvement was not quantified. Only 1 study using vitamin E as monotherapy demonstrated benefit (discussed below). In 2 of the 6 studies, adverse effects such as contact dermatitis, itching, and rash were observed in patients treated with vitamin E.[1]

Limitations of the review included different formulations of vitamin E, lack of standard process in evaluating scar healing, differences in duration and frequency of vitamin E application to wounds, and lack of information on research methodology for the 6 trials. The review concluded that evidence was insufficient to support the use of topical vitamin E as monotherapy for improving scar appearance or wound healing.[1]

The largest study from the systematic review was a 2010 randomized, single-blind, placebo-controlled trial of 428 children 2 to 9 years old who were undergoing elective inguinal surgery for hernia, hydrocele, or cryptorchidism.[2] Topical vitamin E in the form of VEA Lipogel™ or petrolatum-based ointment control was applied to the skin 3 times daily for at least 15 days before surgery, and twice daily for at least 30 days after surgery.

At 6 months after surgery, 96% of patients or parents in the vitamin E group considered the cosmetic results very good, compared with 78% in the control group ($P<.05$). Furthermore, keloids developed in 6.5% of patients in the control group compared with none in the vitamin E group. No reports of wound infections or adverse outcomes were noted in either group.[2]

A 2009 open-label RCT assigned 27 patients with systemic sclerosis (89% female, mean age 53 years) and a total of 86 digital ulcers to local standard ulcer care, with or without the addition of vitamin E gel.[3] Both groups were treated twice a week until healing of the digital ulcers.

Vitamin E induced a faster healing time than standard care (13 vs 20 weeks; $P<.0001$). Limitations of the study included lack of blinding and lack of information on the randomization process.[3]

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Aside from supine sleep position, what interventions are effective in preventing sudden infant death syndrome (SIDS)?

EVIDENCE-BASED ANSWER

Breastfeeding of any duration, breastfeeding at age 2 months or older, and exclusive breastfeeding are all associated with reduced risk of SIDS (SOR: **B**, meta-analysis of case-control studies). Other factors associated with a lower risk of SIDS include pacifier use, especially when used for sleep (SOR: **B**, meta-analysis of case-control studies), fan use during sleep, and room-sharing without bed-sharing (SOR: **B**, case-control studies). However, no data are available on whether recommending these strategies to parents would reduce SIDS cases. Home monitoring does not appear to be effective for reducing SIDS in at-risk infants (SOR: **C**, systematic review of 1 underpowered RCT and 10 prospective cohort studies).

A 2011 meta-analysis of 18 case-control studies (N=4,455) evaluated the relationship between breastfeeding and SIDS risk.[1] Study selection criteria defined by the American Academy of Pediatrics (AAP) SIDS Task Force included having an appropriate definition of SIDS as determined by the reviewers, diagnosis confirmation with autopsies performed in >98% of cases, and age-matched controls. The AAP defines SIDS as the death of an infant less than 1 year of age that remains unexplained after a thorough case investigation.

Any breastfeeding of any duration was associated with a decrease in SIDS risk (odds ratio [OR] 0.4; 95% CI, 0.35–0.44). Infant breastfeeding at 2 months of age or older (OR 0.38; 95% CI, 0.27–0.54) and exclusive breastfeeding for any duration also decreased SIDS risk (OR 0.27; 95% CI, 0.24–0.31).[1]

A 2005 meta-analysis of 7 case-control studies (N=392) analyzed the relationship between pacifiers and SIDS risk.[2] The same selection criteria were used as above.

Multivariate analyses adjusted for factors including sleep position showed a reduction in SIDS risk with pacifier use during last sleep (OR 0.39; 95% CI, 0.31–0.50) and general pacifier use during a period before an infant died (OR 0.71; 95% CI, 0.59–0.85).[2]

A 2008 case-control study (case n=185, control n=312) investigated fan use and SIDS risk in 11 California counties.[3] Cases met the AAP definition of SIDS. Controls matched for county of residence, maternal race, and infant age were randomly selected from eligible birth certificates. Researchers conducted in-person interviews about sleep environment with mothers of case and control infants at a median of 3.8 months after the infant's death.

Fan use during last sleep was associated with reduced SIDS risk (OR 0.28; 95% CI, 0.10–0.77). Fan use was associated with a greater reduction in SIDS risk in warmer room temperatures (OR 0.06; 95% CI, 0.01–0.52), prone or side-sleep positions (OR 0.14; 95% CI, 0.03–0.55), shared bed with nonparent (OR 0.15; 95% CI, 0.01–1.85), and nonpacifier users (OR 0.22; 95% CI, 0.07–0.69).

A 1999 English case-control study (case n=325, control n=1,300) examined unsafe sleeping environments and risk of SIDS.[4] SIDS diagnoses were established by a multidisciplinary committee after autopsy using the Avon clinicopathological system to rule out other causes of death. Infants 7 to 364 days old who died from SIDS were compared with 4 age-matched controls selected from a total regional population of 17 million. Data for sleep habits and demographics was obtained by research interviews and medical records. Families were interviewed within days of the death and again within weeks.

Sleeping in a room alone compared with room sharing without bed sharing increased the odds of SIDS (OR 11; 95% CI, 4–26).[4]

A 2011 systematic review identified 1 RCT and 10 uncontrolled prospective cohort studies (N=2,210) examining the use of home monitoring for reduction of infant mortality.[5] One underpowered RCT compared home monitoring with use of weighing scales as a control for reduction of SIDS in siblings of SIDS infants (n=100). No deaths were recorded in either group over 6 months. The study was designed to assess the feasibility of a larger scale RCT that was never completed. In cohort studies, at-risk infants were monitored for 12,160 months (n=2,110, follow-up range 3.2–10 months). Most infants given monitors had a history of acute life-threatening

events, unexplained apnea, or were siblings of SIDS infants.

There was no significant effect of in-home monitoring. Studies were limited by heterogeneity in the types of home monitors and low rates of infant deaths.[5]

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Does metformin decrease the development of diabetes in children with prediabetes?

EVIDENCE-BASED ANSWER

We do not know the answer yet. No studies have evaluated the development of diabetes in prediabetic children treated with metformin. Metformin therapy does, however, decrease body mass index (BMI), fasting glucose, and fasting insulin levels (SOR: **B**, RCTs).

A 2008 double-blinded RCT (N=120) examined the effectiveness of metformin compared with placebo in reducing body weight and hyperinsulinemia in prediabetic children and adolescents 9 to 17 years old over 6 months.[1] Patients with a BMI of more than the 95th percentile and hyperinsulinemia (defined as midpuberty levels >30 mU/L; postpuberty levels >20 mU/L) were recruited at a Turkish outpatient endocrinology clinic. Exclusion criteria included patients with preexisting diabetes or treatment for hyperglycemia, or other conditions resulting in impaired glucose tolerance. Patients received metformin 500 mg BID or placebo for 6 months, plus an individually catered diet, and an exercise and behavioral therapy program.

Metformin use was associated with a decrease in BMI from 28.5 to 26.7 (P<.001) and fasting insulin levels from 19.2 to 11.1 µU/mL (P<.001), while the placebo group showed no change in BMI (increase from 28.0 to 28.6; P=.339) or fasting insulin levels (decrease from 18.6 to 15.3 µU/mL; P=.06).[1]

A 2013 double-blinded RCT compared the effects of metformin (1 g in the morning and 500 mg at night) with placebo in obese (BMI >95%ile) children and adolescents ages 8 to 18 years with hyperinsulinemia and/or impaired fasting glucose or impaired glucose tolerance (N=151).[2] Participants were recruited from 6 pediatric endocrine centers in the United Kingdom. Outcome measures included reduction in BMI-Standard Deviation Score (BMI-SDS) at 6 months, and insulin and glucose levels from oral glucose tolerance tests at 3 and 6 months.

At 6 months, the metformin group reduced the BMI-SDS by –0.1 SD (3% of the initial BMI-SDS; 95% CI, –0.18 to –0.02, P=.02) compared with no mean change in the placebo group. At 3 months, metformin improved fasting glucose compared with placebo (–2.88 mg/dL; 95% CI, –0.31 to –0.00, P=.047), but this improvement was not sustained at 6 months. Study limitations included a 27% dropout rate, no lifestyle modification arm of trial, and difficulty assessing medication compliance. Adverse events (20 in metformin group, 8 in placebo group, none serious) were mostly related to gastrointestinal adverse events of the medication.[2]

A 2014 Australian RCT (N=85) compared 2 energy-restricted diets (moderate-carbohydrate, increased protein diet vs high-carbohydrate, moderate-protein diet) in children ages 10 to 17 years old with prediabetes.[3] Participants were overweight or obese with either pretype 2 diabetes and/or clinical features of insulin resistance, defined as having a fasting insulin (pmol/L)/glucose (mmol/L) ratio >20 with one or more of the following conditions: acanthosis nigricans, polycystic ovarian syndrome, hypertension, fasting high-density lipoprotein cholesterol less than 1.03 mmol/L, or fasting triglycerides of 1.7 mmol/L or more. All patients received metformin (250 mg BID for 2 weeks, then 500 mg BID) and attended a structured physical activity program. Study outcomes included BMI and percent body fat at 12 months.

Metformin plus either energy-restricted diet reduced BMI by 6.8% (95% CI, 4.9–8.8) and decreased percent body fat by 2.4% (95% CI, 1.3–3.4). No difference in effect size was noted between the 2 diets, although individual data were not

given. Limitations included no comparison groups without metformin, unknown adherence to medication, and lack of baseline dietary intake of participants.

The 2017 American Diabetes Association Guidelines recommend prediabetic metformin for the prevention of type 2 diabetes in high-risk adults, but did not address the use of metformin in prediabetic children.[4]

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Is trauma-focused cognitive behavioral therapy effective in decreasing posttraumatic stress disorder (PTSD) in children and adolescents?

EVIDENCE-BASED ANSWER

Yes. In children and adolescents with PTSD, outpatient trauma-focused cognitive-behavioral therapy (Tf-CBT) is more effective than wait-list controls for reducing PTSD symptoms, and appears more effective than several other therapeutic options (SOR: **A**, based on a systematic review and RCT).

A 2014 systematic review analyzed 10 RCTs (N=1,058) examining the effectiveness of Tf-CBT for reducing mental health symptoms in children and adolescents exposed to trauma.[1] The 10 RCTs compared Tf-CBT delivered in 12 to 16 outpatient sessions with various control groups including wait-list, therapy as usual, or other cognitive-behavioral approaches. Patients 2 to 18 years old had exposure to a broad range of traumatic events such as sexual violence or abuse, witnessed intimate partner violence, hurricane exposure, war exposure, or mixed trauma. Outcomes included changes in PTSD symptoms, depression symptoms, behavioral problems, and other mental health symptoms and function measured at up to 12 months.

Because of study heterogeneity, no pooled analyses were possible; however, 7 of 8 RCTs found a statistically significant difference in effect size of PTSD symptoms as measured by a variety of PTSD symptom scales between Tf-CBT and control groups. Tf-CBT was found to have large effect size (≥0.75) for reducing PTSD symptoms compared with a wait-list control group. Effect size of Tf-CBT was moderate (≥0.4) compared with other active treatment groups, including nondirective supportive therapy, child-centered therapy, or therapy as usual. The single study that compared Tf-CBT with Cognitive-Behavioral Intervention for Trauma in Schools found a reduction in PTSD symptoms in both groups, but no significant difference between groups. Trials were clinically heterogeneous in trauma exposure, type of control group, and outcomes measured. Authors of 7 of the 10 studies were the developers of Tf-CBT.[1]

A 2015 German RCT (N=159) examined the effectiveness of outpatient Tf-CBT for posttraumatic stress symptoms compared with a wait-list control.[2] Patients 7 to 17 years old were recruited or referred to 1 of 8 participating mental health clinics. Patients had exposure to 1 or more traumatic event(s) after age 2, and a score of 35 points or more on the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA). This scale has a maximum of 136 points, with higher scores indicating more severe PTSD. The intervention group received 12 weekly, 90-minute parallel or conjoint sessions with patients and caregivers. The control group did not receive Tf-CBT, but underwent 2 reassessments and were offered delayed trauma-focused treatment after 4 months. The primary outcome was the effect on posttraumatic stress symptoms measured by the CAPS-CA at 4 months. Secondary outcomes included diagnostic status of PTSD, self-reported and caregiver-reported posttraumatic stress symptoms, the Child Posttraumatic Cognitions Inventory (CPTCI), and results of symptom inventories evaluating behaviors, depression, anxiety, and quality of life for participants.

The reduction of the mean CAPS-CA score was 26 points for Tf-CBT 4 months (effect size 1.51) versus 14 points for controls (effect size 0.88). More participants in the treatment group achieved clinical remission of PTSD than in the control group (45% vs 29%; *P*=.031; number needed to treat=6.3). No

adverse events were reported for the intervention. Limitations included short follow-up (4 months) and lack of blinding, as well as a significant difference in parental education favoring the treatment group.[2]

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Does the administration of loop diuretics at the time of blood transfusion prevent transfusion-associated circulatory overload (TACO)?

EVIDENCE-BASED ANSWER

The answer is unknown. In patients identified with TACO, 90% had received loop diuretics before, during, or after receiving blood components. However, mortality was higher in patients receiving diuretics before transfusion than during or after transfusion (SOR: **B**, longitudinal study with cohort analysis). In preterm infants, furosemide given before packed red blood cell (PRBC) transfusion decreases mean FiO_2 compared with baseline (SOR: **C**, systematic review of RCTs with disease-oriented evidence).

A 2015 retrospective longitudinal study (N=1,071) from Ireland evaluated serious transfusion-related reactions reported to the National Haemovigilance Office between 2000 and 2010.[1] More than 2 million blood components were transfused during this time and 221 cases of TACO were reported (84% involved transfusion of red blood cells). Overall, 97% of patients who developed TACO reported preexisting conditions involving the cardiovascular, respiratory, or renal systems. In patients with TACO, 90% had received loop diuretics before (n=43), during (n=34), or after (n=162) transfusion.

Patients receiving diuretics before transfusion had an increased risk of mortality compared with patients receiving diuretics during or after transfusion (odds ratio [OR] 2.5; 95% CI, 1.1–6.0). Study limitations include suspected underreporting of TACO and possible misinterpretation of patients receiving diuretics before transfusion as part of the regular medication regimen or to prevent TACO.[1]

A 2015 systematic review of 4 small RCTs (N=100) examined the effect of loop diuretics compared with placebo, no treatment, or standard fluid restriction in adults and children receiving PRBC transfusions.[2]

In 1 trial of preterm infants (n=20), a single dose of furosemide (1 mg/kg) after completion of PRBC transfusion did not improve multiple pulmonary parameters including minute ventilation, compliance, and resistance compared with placebo. In another trial of preterm infants (n=40), a single dose of furosemide (1 mg/kg) or placebo was given before PRBC transfusion. Lasix led to a decrease in mean FiO_2 compared with baseline while placebo led to an increase; between-group differences in percent change were significant (–0.6% vs 9.1%; $P<.05$).[2]

Two studies enrolled adults. In the first (n=20), a single dose of furosemide 40 mg IV given before transfusion of 1 unit of whole blood decreased pulmonary capillary wedge pressures (from 6.8 to 5.3 mmHg; $P<.001$) while the control group receiving no intervention had an increase in wedge pressure (from 7.8 to 9.4 mmHg; $P<.001$). However, in the second study of adults (n=20), a single dose of furosemide 40 mg IV administered before the start of a 2-unit whole blood transfusion had no effect on wedge pressure (decrease from 8.0 to 7.7 mmHg; $P>.05$) but wedge pressure increased in the control group (from 8.1 to 11 mmHg; $P<.001$). Heterogeneity between the studies precluded meta-analyses, and between-group comparisons were not reported.[2]

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What are the risks and benefits of intrauterine device (IUD) insertion on the same day as office counseling?

EVIDENCE-BASED ANSWER

Risk of pelvic inflammatory disease (PID) does not differ between same-day or delayed insertion for women without overt cervicitis (SOR: **A**, meta-analysis of RCTs and prospective cohort). Same-day insertion increases probability of continued IUD use compared with delayed insertion. However, women with same-day insertion after an induced or spontaneous abortion are more than twice as likely to have IUD expulsion than women with delayed insertion (SOR: **A**, meta-analysis of RCTs). Return rates for a subsequent appointment for IUD insertion are as low as 54% (SOR: **B**, cross-sectional study). Delaying IUD placement for sexually transmitted disease testing is discouraged in asymptomatic patients (SOR: **C**, consensus opinion).

A 2014 meta-analysis of 3 RCTs evaluated women (>16 years old, N=878) assigned to immediate IUD insertion or insertion delayed 2 to 6 weeks after an induced abortion or aspiration and curettage for spontaneous abortion.[1] Trials excluded patients with a recent history of sexually transmitted infection (STI), PID, or signs of acute cervicitis. Outcomes were measured at 6 months after abortion (2 trials) or 6 months after IUD insertion (1 trial). One trial evaluated patients for infection at an 8- to 10-week follow-up visit.

Women with immediate insertion were more likely to be using the IUD at 6 months compared with delayed insertion (3 trials, n=878; risk ratio [RR] 1.4; 95% CI, 1.2–1.6). No difference was noted in infection at 6 months (3 trials, n=878; RR 1.0; 95% CI, 0.33–3.1). The immediate insertion group was more likely to experience IUD expulsion than the delayed insertion group (3 trials, n=878; RR 2.6; 95% CI, 1.2–6.0).[1]

A 2015 prospective cohort study examined the risk of PID among women (15–45 years old, N=272) who presented for pregnancy testing or emergency contraception and chose same-day copper or levonorgestrel IUD insertion (n=28), delayed IUD insertion within 3 months (n=17), and no IUD use (n=227).[2] All patients had urine screening for chlamydia and gonorrhea at presentation. Only patients with no signs of cervicitis (signs not specified) on pelvic examination were offered same-day IUD insertions.

The number of women diagnosed with PID after 3 months did not differ between the IUD groups: 3.6% of women (1 out of 28) with same-day insertion compared with 12% (2 out of 17) with delayed insertion (*P*=.54). Limitations were small size, use of patient-reported outcomes, and patient self-selection into comparison groups.[2]

A 2012 cross-sectional study evaluated Illinois Medicaid patients (mean age 27 years, N=708) for whom an IUD was ordered at 1 clinic visit and then scheduled for placement at a second visit.[3] Nearly half of the women for whom an IUD was ordered did not return for IUD placement (46%). IUD insertion by another provider was unlikely due to local Medicaid policy.

The Centers for Disease Control and Prevention and American College of Obstetricians and Gynecologists have discouraged delaying IUD insertion for STI testing in patients without mucopurulent discharge or known gonorrhea or chlamydia infection.[4,5] The organizations endorsed testing for these infections at the time of insertion for high-risk women due for their annual screening and for women with new risk factors since their last screening. EBP

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A shorter course of DAPT after stenting

Gargiulo G, Windecker S, da Costa BR, Feres F, Hong MK, Gilard M, et al. Short term versus long term dual antiplatelet therapy after implantation of drug eluting stent in patients with or without diabetes: systematic review and meta-analysis of individual participant data from randomised trials. *BMJ*. 2016; 355:i5483.

Patients in this meta-analysis, which included 6 RCTs (N=11,473), underwent placement of a drug-eluting stent (DES) and subsequently received dual antiplatelet therapy (DAPT). DAPT varied by trial. Diabetes was found to be an independent risk factor for major adverse cardiac events after placement of the DES (hazard ratio [HR] 2.3; 95% CI, 1.0–5.3).

Yet in patients with and without diabetes, patients receiving DAPT for 1 year or longer, assessed at 12 or 24 months depending on trial, had similar rates of major adverse cardiac events as patients receiving DAPT for 6 months or less (HR 1.0; 95% CI, 0.62–1.8 for patients with diabetes; HR 0.97; 95% CI, 0.67–1.4 for patients without diabetes). No additional benefit was found for longer term DAPT in both groups in terms of other patient-oriented outcomes, including myocardial infarction (HR 0.95; 95% CI, 0.58–1.5 for patients with diabetes and HR 1.15; 95% CI, 0.68–2.0 for patients without diabetes). An increase in bleeding events was noted in patients receiving longer DAPT regimens, but the increase was not statistically significant.

A major limitation of this meta-analysis was that the individual studies were not designed for a subgroup analysis for diabetes.

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

Bottom line: Important clinical outcomes after DES placement do not differ for patients given 6 months or less of DAPT or 12 months of DAPT. An increase in bleeding events occurred with longer therapy, but the difference compared with bleeding event rates with shorter therapy was not statistically significant. These findings hold for patients with and without diabetes. However, this information may not warrant a change of practice for family physicians, because interventional cardiologists normally make the decisions on length of therapy of DAPT after DES placement.

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No benefit for oxygen in stable COPD with moderate hypoxemia

Long-Term Oxygen Treatment Trial Research Group, Albert RK, Au DH, et al. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med*. 2016; 375(17):1617–1627.

A 2016 multicenter nonblinded RCT (N=738) compared use of supplemental oxygen with no supplemental oxygen for moderate resting desaturation (SpO_2 89%–93%) or moderate exercise-induced desaturation (SpO_2 >80% for >5 minutes and <90% for ≥10 seconds during a 6 minute walk test) in outpatients with stable chronic obstructive pulmonary disease (COPD).

Patients were randomized to receive supplemental oxygen at 2 L/min titrated to maintain SpO_2 >90% at rest and/or during sleep and exercise or to receive no supplemental oxygen. The primary outcome was the composite of death or first hospitalization for any cause. Secondary outcomes included incidence of COPD exacerbations, adherence to supplemental O_2, development of severe resting or severe exercise-induced desaturations, distance walked in 6 minutes, spirometry, and quality-of-life scores.

No difference was noted between the groups in the primary outcome (hazard ratio [HR] 0.94; 95% CI, 0.79–1.1), COPD exacerbations (HR 1.1; 95% CI, 0.98–1.2), or COPD-related hospitalizations (HR 0.99; 95% CI, 0.83–1.2). No significant difference was noted in quality of life, anxiety, depression, lung function, distance walked in 6 minutes, or other functional outcomes between the groups.

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

Bottom line: There is no morbidity or mortality benefit with supplemental oxygen use for patients with stable COPD and moderate resting or exercise-induced hypoxemia. Patients with resting SpO_2 89% to 93% are not typically prescribed supplemental oxygen. EBP

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