**Should you test or treat pregnant women with a history of pregnancy-related VTE?**

**Evidence-based answer**
You probably shouldn’t test, although you may want to treat your patient with low-molecular-weight heparin (LMWH).

No high-quality evidence supports testing for thrombophilia in pregnant patients who have experienced venous thromboembolism (VTE) in a previous pregnancy (strength of recommendation [SOR]: C, expert opinion and extrapolation from studies of nonpregnant patients).

Antepartum and postpartum anticoagulation with LMWH produces lower rates of VTE in patients with a prior history of VTE in pregnancy (SOR: B, based on a prospective cohort study and extrapolation from a meta-analysis of treatment in nonpregnant patients). Pregnant women with a prior history of VTE who are not treated with anticoagulation have about a 5% risk of antepartum or postpartum VTE (SOR: B, based on a prospective cohort study).

Expert opinion recommends graduated compression stockings (SOR: C, expert/consensus clinical opinion).

**Evidence summary**
A population-based cohort study centered in Olmsted County, Minn (N=50,080 births between 1966 and 1995) established a baseline rate of VTE among pregnant patients (105 total events; 0.2% incidence), and found an increased relative risk of VTE among pregnant and postpartum patients (RR=4.29; 95% confidence interval [CI], 3.49–5.22; P<.001) compared with nonpregnant patients. The incidence of VTE was 199.7 per 100,000 woman-years. The postpartum annual incidence of VTE was 5 times higher than antepartum (511.2 vs 95.8 per 100,000).¹

**Thrombophilia testing typically is not useful**
There is no evidence of improved outcomes from screening pregnant women with prior VTEs for some of the more common hypercoagulable conditions, including factor V Leiden, prothrombin G20210A mutation, protein C and S deficiency, and antiphospholipid syndrome.

A recent Clinical Inquiry addressed this question for general medical patients with idiopathic deep venous thrombosis and found no quality evidence to support a thrombophilia work-up in most patients. A subsequent review, which addressed pregnant patients specifically, made the same recommendation; that is, no quality evidence supports a thrombophilia work-up in patients at risk for VTE.

**How effective is prophylactic anticoagulation?**

A meta-analysis in the American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines reviewing data from 1,953 orthopedic and medical patients who were mostly postoperative (and not including pregnant women) found that prophylactic anticoagulation with LMWH for patients at risk for VTE produced a relative risk for recurrent VTE of 0.36 (95% CI, 0.20–0.67).

In a more recent prospective cohort study, prophylactic LMWH was given to 177 of 286 (62% treated) patients according to risk-based scoring for recurrent VTE. The treatment protocol called for anticoagulation antepartum, postpartum, or both, depending on risk score (the higher the risk, the longer the period of thromboprophylaxis). Patients with previous pregnancy-associated VTE received both antepartum and postpartum anticoagulation. The study found recurrent VTE rates of 0.35% (95% CI, 0–1.03) antepartum and 0.7% (95% CI, 0–1.67) postpartum among treated patients.

Data from an earlier report summarized the expected VTE rate in patients not exposed to anticoagulation prophylaxis. This prospective cohort study evaluated 125 pregnant women with a history of prior VTE who had anticoagulation withheld and determined the rate of recurrent antepartum and postpartum VTE. Three women had an antepartum VTE (2.4%; 95% CI, 0.2–6.9). Three additional women developed postpartum VTE, for a total of 6 VTEs (4.8%, no CI reported).

**LMWH is beneficial, but dosing can be tricky**

Patients with a history of pregnancy-associated VTE—whether or not they have known thrombophilia—do benefit from routine ante- and postpartum thromboprophylaxis, per expert opinion in practice guidelines. LMWH is the preferred agent because of its safety during pregnancy and ease of dosing.

Precise dosing is nonetheless difficult to determine because clinical studies in pregnant patients are lacking and renal clearance of LMWH increases during pregnancy. Most authors recommend doses between the prophylactic and therapeutic ranges. Subcutaneous enoxaparin, for example, can be given at 40 mg every 24 hours (more aggressive, thus higher-risk, dosing is as much as 1 mg/kg every 12 hours); dalteparin can be administered at 5,000 units every 24 hours up to as much as 100 units/kg every 12 hours.

**Recommendations**

The American College of Obstetricians and Gynecologists (ACOG) 2011 updated Practice Bulletin recommends thrombophilia testing for pregnant patients previously diagnosed with a pregnancy-associated VTE, although they acknowledge the lack of quality evidence to support this recommendation. ACOG also recommends ante- and postpartum thromboprophylaxis for such patients.

The ACCP expert review recommends that all pregnant women diagnosed with VTE during a previous pregnancy wear graduated elastic compression stockings throughout pregnancy and for at least 6 weeks postpartum.

The ACCP also recommends LMWH for all pregnant patients with a prior VTE. Additionally, the ACCP says that a thrombophilia work-up, while not routinely recommended, might be appropriate—contingent on additional risk assessment.

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REFERENCES
From the Editor

Perfect pitch

Dear EBP Readers,

Not long ago, the US Preventive Services Task Force (USPSTF) published a recommendation advising doctors to stop using the PSA for prostate cancer screening in the general population.\(^1\) This was received with Howls of protest from various experts around the country. Even one of my local physician radio personalities claimed that this was a “dangerous” recommendation.

The USPSTF, however, is no stranger to this sort of attention. In fact, the Task Force was designed to shake things up. Screening recommendations are often generated under the influence of specialty and industry advocacy groups that push for widespread application, often with a bit of a blind eye to the possible harms. The Task Force was convened as a corrective to this tendency.

This cacophony of dissent reminded me of an experience I have had on several occasions singing in a community choir. Community choirs are not usually filled with expert singers. Sure, one lady in the alto section has perfect pitch and was a graduate of Juilliard, but the rest of us are average folks who just like to hang out together and put on a good show. The conductor’s major qualification for leadership is that he owns a tuxedo with tails.

At show time, we get up on stage and start with an a cappella version of the folk song “Oh Shenandoah.” By the time we are crossing the wide Missouri, it is starting to sound like someone scraping fingernails across a blackboard. The director’s eyes widen in growing panic as he realizes we are heading for a polyphonic melt-down.

Everyone starts looking around to see who is out of tune. Pretty quickly we realize that the culprit is the lady with perfect pitch and the truth hits: the whole choir has gone out of tune. She is the only one on the right note. Arrgh! With a touch of indignation, we start to think “Why won’t Miss Juilliard just shut up or go along with the rest of us? Then no one in the audience would notice.”

I suspect certain specialists might be having similar thoughts right now about the USPSTF.

Regards,

Jon O. Neher, MD

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Jon O. Neher, MD
Evidence-Based Practice / June 2013

Diving for PURLs

Acid suppression and enteric infection—a potentially explosive combination

A review examining the association between proton pumps inhibitor (PPI) use and enteric infections included 33 primarily case-control and cohort studies (2 studies for Salmonella, 4 for Campylobacter jejuni, and 27 for Clostridium difficile).

Overall, reviewers found an enhanced susceptibility to enteric infection with PPI use. Patients using PPIs were more likely than patients not using PPIs to be infected with Salmonella (killed at pH<4), RR of infection, 4.2–8.3; C jejuni (killed at pH<6), RR, 3.5–11.7; and C difficile, RR 1.2–5.0.

This study did not include a New England Journal of Medicine article from November 2011 that prompted the FDA to issue a public warning about the link between PPIs and C difficile.

Bottom line: PPIs should be prescribed cautiously to those vulnerable to enteric infections, such as travelers and hospitalized patients.

Review Author and Summary Author: Kohar Jones, MD, The University of Chicago, Department of Family Medicine, Chicago, IL

Very-low-sodium diets in heart failure (HF) patients increase mortality

This meta-analysis of 6 RCTs compared a low-sodium diet (1.8 g/d) with a “normal” sodium diet (2.8 g/d) in 2,747 patients with HF characterized by an ejection fraction of <40%. Patients in the intervention group had reduced symptoms of depression and anxiety at the 6- and 12-month follow-ups.

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

Bottom line: In patients with treatment-resistant depression, the addition of CBT to their current pharmacotherapy is more effective than pharmacotherapy alone.

Review Author and Summary Author: Irene Skowronek, PhD, University of North Carolina, Department of Family Medicine

Cognitive behavioral therapy (CBT) effective in pharmacotherapy-resistant depression

This multisite RCT compared antidepressant treatment augmented with CBT vs antidepressants (usual care) alone. Researchers enrolled 469 patients (18–75 years old) from 73 UK general practices who had been on antidepressants for ≥6 weeks, scored ≥14 on the Beck Depression Inventory (BDI), and met the International Classification of Diseases (ICD)-10 criteria for depression. CBT treatment involved 12–18 50- to 60-min sessions. The primary outcome was response defined as 50% reduction in BDI score from baseline to 6-month follow-up.

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

Bottom line: Instructing patients with heart failure to consume a very-low-sodium diet is associated with increased morbidity and mortality.

Review Author and Summary Author: Anne Mounsey, MD, University of North Carolina, Department of Family Medicine
Cockroft-Gault formula vs modification diet in renal disease formula for calculating renal function in older adults

Bottom line
In hospitalized patients older than 70 years, the Cockroft-Gault (CG) formula generates an estimate of creatinine clearance (CrCl) that is closer to the measured 24-hour creatinine than the modification diet in renal disease (MDRD) formula. The CG tends to slightly underestimate the CrCl, while the MDRD tends to overestimate it.

Evidence summary
Serum creatinine concentration is a poor measure of renal function in older adults because of decreased creatinine production with age. A better assessment of renal function is the CrCl. The CrCl is directly measured with a 24-hour urine collection, or estimated using formulas such as the CG\(^1\) or MDRD.\(^2\)

In 1 comparison study, CrCl was calculated by 24-hour urine measurement and compared with calculations by CG and MDRD in 121 French hospitalized patients \(\geq 70\) years old.\(^3\) All patients had an indwelling Foley catheter for care reasons, were hemodynamically stable, and were not dehydrated. The mean number of comorbidities was 6.5 and body mass index was 22.6 kg/m\(^2\). The TABLE shows the results of the measurement calculations. The CG formula slightly underestimated the CrCl and the MDRD greatly overestimated it. More patients were misclassified into a different renal failure stage with MDRD than CG.

A 2003 study with 52 older patients aged 69–92 years compared 4 different formulas using chromium EDTA as the gold standard.\(^4\) These patients had an average of 3 problems, most commonly vascular disease (n=32), and took an average of 4.5 medications. Most common drugs were diuretics (n=28) and 15 patients took angiotensin-converting enzyme inhibitors. These investigators found CG to be most accurate followed by MDRD. The median creatinine clearance by chromium EDTA was 52.7 mL/min, by CG was 48.5 mL/min, and by MDRD was 63.0 mL/min, with fewer patients misclassified using CG (10 vs 14).

Two other studies\(^5,6\) found the MDRD to be more accurate overall, but used radionuclide markers as a gold standard in a mixed age sample. One study evaluated 122 diabetic patients (age range, 30–83 years) who had renal damage\(^5\) and the other study assessed 107 patients (age range, 39–82 years) with renal dysfunction, most of whom (58%) were dehydrated.\(^6\)

In all, both the CG and MDRD formulas appear to misclassify one-third of older patients into a different renal failure stage. Underestimating renal function (as with CG) may lead to lower medication dosing and treatment failure, while overestimating (as with MDRD) may contribute to medication toxicity and a higher risk of adverse events. At this time, there appear to be no fully reliable shortcuts when knowledge of renal function is critical to management.\(^3\)

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TABLE
Comparison of methods to measure creatinine clearance (CrCl)\(^3\)

<table>
<thead>
<tr>
<th></th>
<th>Measured CrCl</th>
<th>Cockroft-Gault CrCl</th>
<th>Modification of diet in renal disease CrCl</th>
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</thead>
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<tr>
<td>Median CrCl, mL/min</td>
<td>43.8</td>
<td>40.9</td>
<td>61.3</td>
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<tr>
<td>Bias</td>
<td>–3.5±22.5</td>
<td>+20.1±28.2</td>
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<tr>
<td>Misclassification of renal function, %</td>
<td>33.1</td>
<td>49.6</td>
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</table>

REFERENCES
**What is the best treatment for Osgood-Schlatter’s disease?**

**Evidence-Based Answer**

Most patients with Osgood-Schlatter’s disease (OSD) have symptomatic relief from conservative treatment (activity modification, rest, ice, nonsteroidal anti-inflammatory drugs [NSAIDs]) (SOR: B, prospective cohort and case series). Surgical treatment is rarely required, but may be beneficial in skeletally mature patients with symptoms despite conservative measures (SOR: C, case series).

A prospective Saudi Arabian cohort study reported on the effectiveness of conservative or surgical treatment in 261 patients with 1–2 years of OSD (97% males; average age of 16). \(^1\) Conservative treatment consisted of activity modification, rest, and NSAIDs. Overall, 91% of patients responded well to conservative treatment. Twenty-four patients (9%) underwent surgery: 3 were bilateral surgeries and all returned to normal activity after 3–6 weeks without complications. A limitation of this study is that “responded well” was not explicitly defined.

A retrospective case series of 118 patients with clinical and radiographic documentation of OSD found that 88% of those treated nonoperatively with intermittent activity limitation or immobilization in a cylinder cast reported improved pain or healing at follow-up. \(^2\) Approximately 12% of patients showed no improvement and underwent surgical excision of an ossicle, some combined with a tubercle-thinning procedure. The mean age at surgery was 14.3 years for female patients and 17 for male patients. All but 1 patient had complete relief of symptoms and returned to full activity at 6 weeks.

A retrospective analysis of 107 military recruits who had surgery for unresolved OSD sought to assess long-term outcomes. \(^3\) Surgery was recommended if the patient had radiographic and clinical evidence of OSD, a duration of symptoms long enough to demonstrate severity, if the patient could not continue military training because of failing conservative treatment, or if the patient was unable to kneel or squat without persistent pain during military service. Key outcomes included the Kujala scale (a 13-item knee-specific self-report questionnaire with a scale of 0–100; 95–100 points is considered excellent) and a 100-mm visual analog pain scale (VAS).

After a 10-year follow-up, 87% reported they could participate without restriction in daily work activities (median Kujala score 95 and median VAS score of 7 mm). Seventy-five percent of patients regained their preoperative sports activity level. Thirty-eight percent reported an ability to kneel without pain. Minor postoperative complications occurred with 6 patients, and 2 patients required reoperation.\(^3\)

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**What treatments are effective for chronic prostatitis?**

**Evidence-Based Answer**

Alpha-blockers, antibiotics, or a combination of the 2 are effective treatment options for chronic prostatitis (SOR: A, systematic review of RCTs). Silodosin also reduces chronic prostatitis symptoms. Dutasteride improves prostatitis-related symptoms in older men who have an increased prostate-specific antigen level and negative biopsies (SOR: B, single RCTs).

A systematic review and meta-analysis in 2011 reviewed 23 RCTs (N=2,315) comparing chronic prostatitis symptom scores and treatment response among multiple therapies. \(^1\) Mean ages of participants were from 29 to 56 years, with treatment duration from 4 to 52 weeks.

Compared with placebo, mean total National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) scores (which range from 0 to 43) at follow-up were significantly lower for alpha-blockers (5 trials, N=568; weighted mean difference [WMD] −11.0; 95% CI, −14 to −8.1), antibiotics (3 trials, N=215; WMD −9.8; 95% CI, −15 to −4.6), alpha-blockers plus antibiotics (3 trials, N=382; WMD −14; 95% CI, −18 to −10), and finasteride (2 trials, N=105; WMD −4.6; 95% CI, −8.7 to −0.5). Alpha-blockers plus antibiotics were better than any other therapy and were significantly better than alpha-blockers alone (13 trials, N=1,541; WMD −2.9; 95% CI, −5.2 to −0.5). \(^1\)
A separate RCT compared silodosin with placebo in symptom relief in chronic prostatitis, randomizing 151 patients to receive silodosin 4 mg, silodosin 8 mg, or placebo for 12 weeks. Silodosin 4 mg was associated with a significantly larger decrease in NIH-CPSI score compared with placebo (–12 vs –8.5; \( P = .02 \)). There were no additional treatment benefits with the 8-mg dose.

Another RCT evaluated the efficacy of dutasteride for prostatitis symptoms in 5,379 men with elevated PSA and negative prostate biopsy. After 48 months of taking either dutasteride 0.5 mg/d or placebo, there were modest but statistically significant differences in total NIH-CPSI scores for the dutasteride group (–0.038 vs +0.92; \( P < .0001 \)).

Finally, a RCT evaluated the effectiveness of pregabalin in reducing chronic prostatitis symptoms. The trial enrolled 324 men with symptoms who were randomized to pregabalin titrated up to 600 mg/d or placebo for 6 weeks. The pregabalin group did not have significantly more patients with at least a 6-point decrease in NIH-CPSI score at 6 weeks compared with placebo (47% vs 38%; \( P = .07 \)).

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Are inhaled steroids effective in treating a postviral cough?

Evidence-Based Answer
No. Inhaled corticosteroids do not appear to be effective in reducing postviral cough (SOR: B, small RCTs).

A small prospective RCT from Thailand examined the effectiveness of inhaled budesonide (400-mcg puff BID) in 30 nonasthmatic, nonsmoking adults with persistent post-upper respiratory infection (URI) cough lasting more than 3 weeks. Both a subjective symptom score (1–18 points) and pulmonary function tests were used to assess effectiveness of treatment at 2 and 4 weeks after treatment.

There was no difference in the mean change of symptom score from baseline to 2 weeks (1.6 in the budesonide group vs 1.3 in the placebo group; \( P = .33 \)) or from baseline to 4 weeks (1.4 vs 1.0, respectively; \( P = .33 \)). Similarly, the 2 groups showed no significant difference in forced expiratory volume in 1 second (FEV1), forced vital capacity, or forced expiratory flow after 4 weeks of treatment.

A double-blind placebo-controlled RCT of 56 adolescents in Korea evaluated the change in methacholine dosing necessary to produce a 20% fall in FEV1 with the use of inhaled corticosteroids or placebo post-URI. Patients were included if they had a previous diagnosis of asthma but no use of asthma medications in 2 years, a baseline FEV1 >70% of predicted, and a concentration of methacholine producing a 20% fall in FEV1 <8 mg/mL.

These patients were divided into an experimental group who received inhaled budesonide two 200-mcg puffs BID and a placebo group who received two 500-mcg puffs BID of micronized lactose. Every 3 months over a 9-month period, every patient underwent spirometry and a methacholine challenge test. The budesonide group did not show a statistically significant change in bronchial hyperresponsiveness or in FEV1 compared with the placebo group.

A Cochrane review of 5 RCTs (N=339) examined the effectiveness (primarily defined as decreasing use of oral steroids or emergency department visits) of inhaled steroids in children with episodic viral wheeze and no history of asthma. One trial described in the review found that nebulized budesonide (400 mg 4 times a day \( \times \) 2 days, then BID \( \times \) 7 days) in 52 children with viral-induced wheeze resulted in a decrease in a lower respiratory symptom score (weighted mean difference –0.17; 95% CI, –0.34 to –0.003) compared with placebo. However, cough was not specifically discussed.

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How should we manage metformin-induced diarrhea?

**Evidence-Based Answer**

To minimize metformin-induced diarrhea, patients should be initiated on 500 mg once or twice daily or 850 mg once daily of immediate-release metformin (metformin-IR), which should be slowly titrated over several weeks depending on patient response until the goal dose is reached (SOR: C, consensus guidelines). Switching patients who are unable to tolerate metformin-IR to the extended-release (XR) formulation may improve gastrointestinal (GI) symptoms (SOR: B, retrospective cohort study).

A double-blind RCT (N=451) examined dose-related effects of metformin in patients with type 2 diabetes. Patients were randomized to receive placebo, or 1 of 5 metformin daily doses (500, 1,000, 1,500, 2,000, or 2,500 mg) over an 11-week period. To achieve blinding, all patients received matching placebo as needed, so all patients were taking 5 pills a day. All patients started out taking 1 tablet 3 times daily (metformin 500 mg or placebo). Over 3 weeks patients were escalated to 2 tablets with breakfast, 1 with lunch, and 2 with dinner to achieve their final dose of metformin.

The difference in diarrhea incidence between any metformin dose and placebo was 15% versus 5% (P=.02; NNH=10). No linear relationship with diarrhea incidence was seen with doses above 500 mg. The percentage of patients with diarrhea was 21%, 12%, 19%, and 14% for doses of 1,000, 1,500, 2,000, and 2,500 mg, respectively. The trend toward improved tolerance among higher doses was attributed to weekly dose escalation.

**In healthy individuals with uncomplicated acute open fractures of the distal phalanges, are prophylactic antibiotics necessary for preventing infection?**

**Evidence-Based Answer**

No. The addition of antibiotics to a treatment regimen including aggressive irrigation and debridement does not decrease the risk of infection in healthy adults with open distal phalangeal fractures (SOR: B, meta-analysis).
and fracture stabilization) did not prevent early wound infections (RR 0.56; 95% CI, 0.26–1.2) and none of the treatment or control group patients developed osteomyelitis.\(^1\)

Of the studies included in the Cochrane subgroup concerned with open finger fractures, only 1 was a randomized, placebo-controlled double-blind study with a low risk of bias.\(^2\) (The other 2 studies had concerns for bias due to questions regarding blinding and allocation concealment.) A total of 193 patients older than 16 years of age with open fractures limited to the distal phalanx received meticulous wound care and primary closure and were then randomized to receive prophylactic antibiotics (flucloxacillin 500 mg 4 times daily) or placebo. Patients with wounds sustained more than 12 hours ago, diabetes, oral steroid therapy, fractures caused by bites, symptomatic peripheral vascular disease, or allergy to penicillin, were excluded, as were patients already taking antibiotics. No significant difference in infection rates occurred in patients receiving antibiotics (3%) compared with placebo (4%). No patients developed osteomyelitis or deep wound infection.

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How effective is hypnosis in promoting smoking cessation?

Evidence-Based Answer

It is unclear. In small studies, hypnosis has had mixed results compared with placebo, while also testing comparable to other interventions (No SOR given).

A systematic review with search dates prior to February 2005 examined the effectiveness of hypnosis for tobacco cessation in 9 RCTs with at least 6 months follow-up and biochemically validated abstinence.\(^1\) Comparisons in the included studies were hypnosis versus wait list/no treatment; hypnosis versus attention placebo/advice; hypnosis versus psychological treatments; hypnosis versus rapid/focused smoking; and hypnosis plus group therapy versus group therapy alone.

In the trials that could be combined, no difference was noted between hypnosis and psychological treatments (2 trials, N=211; OR 0.92; 95% CI, 0.42–2.0) or hypnotherapy and rapid/focused smoking (2 trials, N=54; OR 1.0; 95% CI, 0.32–3.1). The authors concluded that the evidence was not conclusive that hypnosis was better than placebo treatments, no treatment, or alternative treatments for smoking cessation.\(^1\)

In a subsequent RCT, 286 smokers were randomly assigned to either behavioral counseling or hypnosis.\(^2\) Both interventions were combined with nicotine patches. Participants in both treatment groups attended two 60-minute sessions, had 3 follow-up phone calls, and used 2 months of nicotine patches. No difference was noted between the groups in reported abstinence at 6 months (29% of the hypnosis group vs 23% of the behavioral counseling group; \(P=.27\)) or at 12 months (24% vs 16%, respectively; \(P=.13\)). Based on biochemical confirmation, there was no difference between groups in abstinence at 6 months (26% vs 18%; \(P=.14\)) or 12 months (20% vs 14%; \(P=.25\)).

Another subsequent RCT examined smoking cessation in 20 smokers randomly assigned to either intensive hypnotherapy (8 hourly sessions and daily self-hypnosis) or to wait-list control (self-help material given and encouraged to set a quit date).\(^3\) Participants were evaluated at the end of treatment and at 3 and 6 months. Self-reported abstinence was confirmed biochemically with carbon monoxide values.

Cessation rates were found to be greater for the intervention group compared with the control group at all time points (40% vs 0% at the end of treatment, \(P<.05\); 60% vs 0% at 12 weeks posttreatment, \(P<.005\); and 40% vs 0% at 26 weeks posttreatment, \(P<.04\)).\(^3\) This study’s weaknesses included a small sample size and the lack of description about the randomization method.

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What is the best initial treatment for hypertension among persons of Hispanic ethnicity?

Evidence-Based Answer
In Hispanic patients with hypertension, initial treatment with commonly available medications (as recommended by JNC 7) works as well as in other ethnic groups (SOR: B, single RCT). Combination drug therapy and intensive drug treatment can provide a greater decrease in systolic blood pressure (BP) than moderate treatment (SOR: C, disease-oriented evidence).

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) only provides general population guidelines for BP treatment.1 Management of Hispanic patients is not differentiated from other groups.

The 2007 ALLHAT study was a large, double-blind RCT that included 6,329 (19%) self-identified Hispanic blacks and whites.2 Its purpose was to determine whether angiotensin-converting enzyme inhibitors, calcium channel blockers, or alpha-blockers were superior to thiazide diuretics in preventing hypertension-related cardiovascular complications. A subanalysis of the ALLHAT study evaluated BP control differences among Hispanics and non-Hispanics older than 55 years who had hypertension and 1 or more cardiovascular heart disease risk factors in an environment with access to high-quality hypertension care.

At 2 years, compared with non-Hispanic whites, Hispanic whites had a 20% greater odds of reaching BP control (OR 1.2; 95% CI, 1.1–1.3) and Hispanic blacks had similar odds of reaching BP control (OR 1.0; 95% CI, 0.86–1.3). Authors concluded that as long as patients had equal access to medical care and medication was available at no cost, adequate BP control in Hispanics was achievable with commonly available medications.2

A 2011 post hoc analysis of a 12-week, randomized, double-blind parallel-group study (N=728) evaluated treatment response among white, African American, and Hispanic patients with previously uncontrolled hypertension (mean systolic BP 150–200 mmHg) on no therapy or monotherapy (an angiotensin receptor blocker).3 They were randomized to receive amlodipine/valsartan intensive (10/320 mg) or moderate (5/160 mg) combination therapy.

In Hispanic individuals at 4 and 12 weeks, a significant decrease was noted in the mean systolic BP in the intensive group (−5.9 mmHg; 95% CI, −9.9 to −2.0; P=.0037) compared with the moderate combination, but no difference was noted in the mean diastolic BP (−2.2 mmHg; 95% CI, −4.83 to 0.46; P=.10).3

A 2008 randomized, open-label, community-based trial compared combination therapy with monotherapy in Hispanic subjects.4 Eligible Hispanic patients (N=109) with stage 2 hypertension (systolic BP ≥160 mmHg and/or diastolic BP ≥100 mm Hg) were given either valsartan/HCTZ (160/12.5 mg/d) or valsartan (160 mg/d) for 2 weeks then titrated to valsartan/HCTZ 320/12.5 mg/d or valsartan 320 mg/d for an additional 4 weeks. The primary end point was a mean change in systolic BP. The combination group did not have a significantly greater decrease in mean systolic BP at 6 weeks compared with monotherapy (−21.7 vs −16.3 mmHg; P=.07).

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What interventions are safe and effective for adults with chronic sinusitis?

Evidence-Based Answer
Topical intranasal steroid (INS) improves symptom scores in adults with chronic rhinosinusitis (CRS). Nasal saline irrigation improves symptoms better than no treatment, but is not as effective as INS. Endoscopic sinus surgery does not appear to offer benefit superior to medical treatment (SOR: A, Cochrane reviews). The addition of antibiotics to INS therapy appears to speed recovery of CRS (SOR: B, single RCT).

A Cochrane review evaluating topical INS for treatment of CRS considered 5 RCTs (N=286).1 Compared with placebo, INS improved self-reported symptom scores.
Another Cochrane review compared various nasal saline irrigation regimens for CRS. Nasal saline irrigation was found to be better than no treatment (3 RCTs, N=129; SMD –1.4; 95% CI, –1.0 to –1.8; P<.00001). Hypertonic versus isotonic saline demonstrated no significant difference in symptom scores (3 RCTs, N=80; SMD 0.34; 95% CI, –0.11 to 0.80; P=.14). INSs were more effective than saline (1 RCT, N=21; SMD –3.3; 95% CI, –5.5 to –1.06; P=.004 vs isotonic saline and SMD –2.9; 95% CI, –4.9 to –0.8; P=.006 vs hypertonic saline).

A double-blind placebo-controlled RCT including 95 adults (mean age 40 years, 68% female) compared antibiotic therapy with or without INS for CRS therapy. Forty-seven patients used 2 puffs (total dose 200 mcg) of fluticasone nasal spray and 48 patients used 2 puffs of placebo, each for 21 days. All participants also used 2 puffs of the decongestant xylometazoline hydrochloride twice daily for 3 days and cefuroxime axetil 250 mg orally twice daily for 10 days. Patients were contacted by telephone at 10, 21, and 56 days for report of any adverse effects or treatment failure. Eighty-eight (93%) patients completed follow-up.

Patients receiving cefuroxime and INS achieved a significantly higher rate of symptom resolution than patients receiving cefuroxime without INS (94% vs 74%; P=.009). Patients receiving INS also achieved symptomatic improvement more rapidly (6.0 vs 9.5 days; P=.01).

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after treatment \((P=.05)\). No patient experienced any serious adverse effects or discontinued treatment.²

Canadian evidence-based guidelines for acute and chronic rhinosinusitis state that topical antibiotics provide modest to no benefit and have only been evaluated in post-FESS patients.³ They did not explicitly provide a recommendation.

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What are the benefits and risks of using diuretics in patients with chronic kidney disease?

Evidence-Based Answer

The risk of cardiovascular disease (CVD) and heart failure is lower with thiazide diuretics compared with other antihypertensive agents in patients with a glomerular filtration rate (GFR) <60 mL/min/1.73m² (SOR: B, based on a single RCT). Loop diuretics are associated with an increased risk of secondary hyperparathyroidism, an effect not seen with thiazides. Lower potassium levels are associated with higher mortality (SOR: C, based on cohort study of disease-oriented outcomes).

A subanalysis of a randomized, double-blind controlled trial, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), compared the combined CVD and heart failure risks between lisinopril (10–40 mg/d) and chlorthalidone (12.5–25 mg/d) over a 6-year period.¹² Subjects were ≥55 years old with hypertension and 1 or more risk factors for CVD. Patients with a GFR <60 mL/min/1.73m² (N=5,662) were found to have an increased risk of CVD (HR 1.1; 95% CI, 1.0–1.3) and heart failure (HR 1.3; 95% CI, 1.1–1.6) when taking lisinopril compared with chlorthalidone.

A multicenter, prospective cross-sectional study (N=3,616) examined urinary excretion of calcium, parathyroid hormone (PTH) levels, and secondary hyperparathyroidism with diuretic use.⁵ Patients were 21 to 74 years old with an estimated GFR of 20–70 mL/min/1.73m². Adjusted urinary calcium excretion was increased with loop diuretic therapy to 55 mg/d (95% CI, 51–60), compared with 40 mg/d (95% CI, 37–42) with no diuretic therapy \((P<.001)\). PTH levels were found to be higher with furosemide monotherapy (82 pg/mL; range, 52–130 pg/mL) compared with thiazide monotherapy (45 pg/mL; range, 31–74 pg/mL), combination therapy (57 pg/mL; range, 37–96 pg/mL), and no therapy (44 pg/mL; range, 30–60 pg/mL) \((P<.001\) comparing furosemide with no diuretic therapy, no significant difference between thiazide and untreated groups). Secondary hyperparathyroidism was defined as PTH ≥65 pg/mL, and was significantly higher in the furosemide group compared with nonusers in patients with CKD stages 2–3 (54% vs 23%) and stage 4 (81% vs 66%) \((P<.05\) for both comparisons).

A prospective observational study enrolled 834 patients (mean age 60.5 years) with stages 3–5 CKD to examine the relationship between serum potassium and mortality in CKD.⁴ Diuretic use was associated with lower potassium levels. Patients with serum potassium level <4 mmol/L had an increase in end-stage renal disease (ESRD) compared with patients with normal levels of potassium (HR 1.9; 95% CI, 1.3–2.3). Patients with a serum potassium level of <3.4 mmol/L had a higher mortality rate than patients with a potassium level of 5 mmol/L (HR 2.4; 95% CI, 1.1–5.1). A correlation may exist between the hypokalemic effects of certain diuretics and an increase in ESRD and mortality.

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2. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA. 2002; 288(23):2981–2997. \([\text{LOE 1b}]\)

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Should women be screened for postpartum hypothyroidism?

**Bottom line**

There are no RCTs or Cochrane reviews to guide whether to screen for postpartum thyroiditis. Organizations including the US Preventive Services Task Force (USPSTF), the American College of Obstetricians and Gynecologists (ACOG), the Endocrine Society, and the American Thyroid Association (ATA) have noted that evidence is insufficient to screen all women for postpartum thyroiditis. Yet, postpartum thyroiditis is common and should be considered in women with symptoms including low energy, postpartum blues or depression, weight gain, cold intolerance, palpitations, abnormal bleeding, and poor milk production.

**Evidence summary**

Postpartum thyroiditis typically progresses from transient thyrotoxicosis to transient hypothyroidism and eventually back to normal thyroid activity. Postpartum thyroiditis develops in approximately 8% (range, 1.1%–16.7%) of pregnant women, and 10% to 20% of women with postpartum thyroiditis develop permanent hypothyroidism.

There are no RCTs for an evidence-based recommendation whether to screen for postpartum thyroiditis. A cohort study of 605 asymptomatic women found postpartum thyroiditis developed in 7.8%. Of these women, only 11% had permanent hypothyroidism. No patients needed therapy for thyrotoxicosis, and only 40% who developed hypothyroidism required treatment. Based in part on these findings, ACOG recommended against universal screening for postpartum thyroiditis.

Other organizations also recommend against screening all postpartum women for thyroid abnormalities, including the USPSTF, the Endocrine Society, and the ATA.

However, according to ACOG, assessment for postpartum thyroiditis with thyroid-stimulating hormone (and perhaps a reflexive free T4) should take place when indicated by history or physical examination. Signs and symptoms that may prompt screening include low energy, postpartum blues or depression, weight gain, cold intolerance, palpitations, abnormal bleeding, and poor milk production. Most of these findings are common in postpartum women and providers—in collaboration with their patients—can decide whether evaluation for postpartum thyroiditis is warranted.

**REFERENCES**


What is the best oral antifungal for treating tinea capitis?

Bottom line
Griseofulvin is more effective than terbinafine for treating tinea capitis caused by Microsporum species, and terbinafine is more effective than griseofulvin for Trichophyton species (SOR: B, subgroup analysis within a meta-analysis). The relative potencies of itraconazole and fluconazole against tinea capitis caused by Trichophyton are unclear.

Evidence summary
Tinea capitis (scalp ringworm) is a common dermatophyte infection found primarily in children. The 2 most common dermatophytes are Microsporum species, which fluoresce green under Wood’s ultraviolet lamp, and Trichophyton species, which do not fluoresce. Topical antifungals are largely ineffective due to the ability of the dermatophytes to burrow deep within the hair follicle shaft beneath the stratum corneum.1,2

In 2011, a meta-analysis of 7 RCTs compared the complete cure rate of tinea capitis with griseofulvin versus terbinafine in 2,163 patients ages 1 to 65 years, most of whom were children.1 There was no significant difference in overall efficacy between griseofulvin (mean duration of treatment 8 weeks; 10–20 mg/kg per day) and terbinafine (mean duration of treatment 4 weeks; 62.5–250 mg/d) (OR 1.2; 95% CI, 0.78–1.9).

Further subgroup analysis of this 2011 meta-analysis did demonstrate a significant difference in cure rate when the dermatophyte was identified. Terbinafine was more efficacious than griseofulvin in treating Trichophyton species (4 trials; N=1,388; OR 1.6; 95% CI, 1.3–2.1). Terbinafine was less efficacious than griseofulvin in treating Microsporum species (3 trials; N=426; OR 0.41; 95% CI, 0.3–0.7).

A 2007 Cochrane review of 21 RCTs assessed the efficacy of systemic antifungal treatment for tinea capitis in 1,812 children caused by Trichophyton species.2 There was no significant difference in cure rates comparing griseofulvin (duration of treatment 6 weeks; 20 mg/kg per day) with itraconazole (duration of treatment 2–3 weeks; 5 mg/kg per day) (1 trial; N=100 children; RR 0.89; 95% CI, 0.76–1.0). There was also no significant difference in cure rates comparing itraconazole (duration of treatment 2–3 weeks; 5 mg/kg per day) with terbinafine (duration of treatment 2–3 weeks; 62.5–250 mg/d) (2 trials; N=160 children; RR 0.93; 95% CI, 0.72–1.2). Lastly, there was no significant difference in cure rates between fluconazole (duration of treatment 2–4 weeks; 5–6 mg/kg per day) and griseofulvin (duration of treatment 6 weeks; 15–20 mg/kg per day) (2 trials; N=140 children; RR 0.92; 95% CI, 0.80–1.1).

REFERENCES
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1. The best rapid estimation of renal function in stable, well-hydrated hospitalized patients older than 70 years is:
   - a. Serum creatinine measurement
   - b. The Cockroft-Gault formula
   - c. The Modification diet in renal disease (MDRD) formula
   - d. Serum cystatin C measurement

2. Initial treatment for suspected Osgood-Schlatter disease consists of all of the following strategies except
   - a. Rest
   - b. Anti-inflammatory medication
   - c. Continued activity until resolution of pain
   - d. Activity modification

3. Which of the following treatments appears most effective for treating symptoms of chronic prostatitis?
   - a. Placebo
   - b. Pregabalin alone
   - c. Alpha-blockers plus antibiotics
   - d. Alpha-blockers alone

4. Which of the following statements is true regarding inhaled steroids for treating a postviral cough?
   - a. Inhaled steroids have been shown to reduce symptoms of cough in all patients experiencing postviral symptoms
   - b. Inhaled steroids have not been shown to reduce postviral cough
   - c. Inhaled steroids have been shown to reduce the duration of all postviral symptoms, but only in patients with a history of asthma
   - d. Inhaled steroids prolong cough in nonsmoking, nonasthmatic patients after an upper respiratory infection

5. Which of the following statements is true regarding metformin?
   - a. More patients experience diarrhea with lower doses
   - b. The extended-release formulation has improved gastrointestinal tolerability
   - c. Patients should be started on metformin using the maximum dose
   - d. Patients will often switch to the immediate-release formulation to relieve gastrointestinal adverse effects

6. Two hours ago a 25-year-old healthy man hit his finger with a hammer and sustained an open fracture to the distal phalanx of his right index finger. After thoroughly irrigating and debriding, the wound, which antibiotic is necessary to decrease his risk of developing an infection of the finger?
   - a. Florofoxacinil
   - b. Ampicillin
   - c. Vancomycin
   - d. No antibiotics are needed

7. How effective is hypnosis as a treatment for smoking cessation?
   - a. Very effective (>90% abstinence rates at 6 months)
   - b. More effective than counseling
   - c. There is no conclusive evidence that hypnosis is effective
   - d. More effective than group therapy

8. A 58-year-old Hispanic man has the following blood pressure readings on several office visits: 158/96, 152/95, 155/94 mmHg. He denies any symptoms and has no other medical conditions. In considering initial therapy, which of the following statements is true?
   - a. Following the JNC-7 guidelines is appropriate
   - b. Only beta-blockers have been found effective
   - c. No treatment is necessary
   - d. Starting with 3 agents would be appropriate
To find an additional 16 pages of HelpDesk Answers content, please visit www.fpin.org/electronic and view the June electronic edition.
Do we need to worry about heparin-induced thrombocytopenia with low-dose prophylactic heparin?

Evidence-Based Answer

The absolute risk for heparin-induced thrombocytopenia (HIT) is 0.2% with low-molecular-weight heparin (LMWH) compared with 2.6% for unfractionated heparin (UFH) for deep venous thrombosis (DVT) prophylaxis in postsurgical patients (SOR: A, meta-analysis of RCT and cohort studies). In nonsurgical patients, the incidence of HIT with LMWH use is 0.8%, with an increased risk with previous exposure (SOR: B, prospective cohort study).

HIT, a type II immune reaction triggered by exposure to heparinoids, is defined as a platelet count of <150,000 (or a 50% decrease from baseline) in the presence of anti-heparin platelet factor 4 antibodies. Known risk factors of HIT include therapeutic heparinoid dosing, duration of therapy longer than 4 days, postsurgical status, female sex, and previous exposure.¹²

A 2007 meta-analysis identified 5 independent trials (N=3,492) evaluating risk of HIT in postsurgical patients who were treated with LMWH or UFH for thromboprophylaxis.³ To be included, studies had to compare prophylactic doses of UFH and LMWH. One analysis grouped the 2 RCTs (N=1,014) and a second grouped the RCTs and 3 nonrandomized prospective case-control studies (N=2,478).

Both analyses found that LMWH had a lower incidence of HIT than UFH (OR 0.10; 95% CI, 0.01–0.82; P=.03 for RCT-only analysis; OR 0.10; 95% CI, 0.03–0.33; P<.001 for mixed-study analysis). Using the second analysis, the absolute risk of HIT with LMWH was 0.2% (95% CI, 0.1–0.4%) and with UFH was 2.6% (95% CI, 1.5%–3.8%) (NNT=42).³

A retrospective chart review of 24,068 patients (50% medical, 48% surgical, 2.2% unclassified) found the incidence of HIT with UFH (subcutaneous and intravenous [IV]) to be 0.2% (49 of 24,068 patients), with HIT occurring more frequently in surgical patients (69% vs 31%; no P value reported).¹ In this review, 60% of patients were being treated for thromboprophylaxis with subcutaneous heparin only and the incidence of HIT with subcutaneous heparin was <0.1% (6 of 14,368 patients) compared with 0.76% (41 of 5,415 patients) with therapeutic IV UFH (no P value reported).

A multicenter prospective cohort study evaluated the incidence of HIT in 1,754 nonsurgical patients (47% hospitalized, 53% ambulatory) who were given either prophylactic low-dose LMWH (21%) or treatment of arterial or venous thromboembolism with therapeutic doses LMWH (42%) or an intermediate dose (fixed or
adjusted to body weight) (37%). The overall incidence of HIT in all dosing groups combined was 0.8% (14 of 1,754) in the first 2 weeks, and was more common in those previously exposed to UFH or LMWH (1.7%) compared with those who had not been previously exposed (0.3%) (OR 4.9; 95% CI, 1.5–16). The incidence of HIT was not affected by dosing of LMWH in the subgroup analysis.

Is nedocromil sodium effective in preventing asthmatic attacks in patients with a history of asthma?

**Evidence-Based Answer**

Regular use of nedocromil sodium is less effective than inhaled steroids and does not reduce asthma exacerbations or episode-free days. Nedocromil does make patients with asthma feel better, modestly reducing asthma symptom scores (SOR: A, systematic review of RCTs).

Production of nedocromil sodium was discontinued in 2008 and has not been available in the United States since 2010.

A 2010 Cochrane database systematic review compared the safety and efficacy of inhaled nedocromil sodium with placebo in the treatment of chronic asthma in children.\(^1\) Fifteen RCTs including 1,422 children (aged 0–18 years) with both short-term (4–24 weeks) and long-term (4–6 years) follow-up were reviewed. Two studies reported on the difference in number of days without asthma symptoms between nedocromil and placebo.

A short-term study (24-week follow-up) with 93 subjects comparing nedocromil with placebo showed a significant difference in the percent of days without symptoms for the nedocromil group (mean difference [MD] 12%; 95% CI, 1.5–22; \(P=.027\)); however, a larger study (n=730) with longer follow-up (4.8 years) found no significant difference between nedocromil and placebo in episode-free days per month (9.3 and 9.3 days/month).\(^1\)

Secondary outcome measures of the Cochrane database systematic review included asthma exacerbations. Overall, parents felt placebo was less efficacious than nedocromil (4 trials, N=301; OR 0.5; 95% CI, 0.3–0.8). There was a small decrease in an asthma daily symptom score among all severity of asthma with nedocromil (5 trials, N=270; MD -0.44; 95% CI, -0.69 to -0.19), and a decrease in daily beta2-agonist use in mild to moderate asthma (2 trials, N=43; MD -0.96; 95% CI, -1.4 to -0.48). There were no differences in reduction in urgent care visits per year (1 trial, N=730; OR 0.97; 95% CI, 0.5–1.9) or lower rates of prednisone use per year (1 trial, N=730; OR 1.2; 95% CI, 0.86–1.6). There was no significant differences in withdrawal from the study due to asthma exacerbations between nedocromil versus placebo (risk ratio [RR] 0.75; 95% CI, 0.33–1.7).\(^1\)

A long-term (4 year) follow-up RCT (N=1,041 children aged 5–12 years) comparing twice-daily inhaled budesonide (200 mcg), twice-daily inhaled nedocromil (8 mg), and placebo assessed the association of asthma symptoms and persistent asthma symptoms with asthma exacerbations (defined as episode requiring ≥3 days use of oral corticosteroids, hospitalization, or emergency department visit due to asthma) by reviewing diary cards that were completed by children on a daily basis.\(^2\) Fewer patients in the budesonide group experienced 1 or more severe exacerbations than patients in the nedocromil group (21% vs 30%, respectively; \(P<.001\)) or the placebo group (21% vs 37% respectively; \(P<.0001\)). There was no statistical significant difference in asthma exacerbations between nedocromil and placebo (30% vs 37%; \(P=.085\)).

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


Is chromium supplementation effective in the management of type 2 DM?

Evidence-Based Answer
Chromium supplementation appears to lower glucose levels and HbA1c in patients with poorly controlled type 2 diabetes (SOR: C, disease-oriented outcomes).

A 2007 systematic review of 41 RCTs (N=1,198) investigated the effectiveness of chromium picolinate on improving HbA1c and fasting sugar in patients with poorly controlled diabetes. Chromium picolinate lowered HbA1c by 0.6% (95% CI, –0.9 to –0.2) and fasting blood sugar by 1.0 mmol/L (95% CI, –1.4 to –0.5) compared with placebo. Limitations of the studies included inconsistent reporting of chromium formulations, dosages, and type of participant’s diabetes. Also, several studies were supported by the food or supplement industry.

In 2008, a randomized, double-blind, placebo-controlled study was conducted to evaluate efficacy and safety of the combination of chromium picolinate and biotin on glycemic control of 440 patients with poorly controlled diabetes (HbA1c ≥7%) taking oral antidiabetic (OAD) medication. The treatment group took chromium picolinate (2 mg/d) as an adjunct to an OAD regimen for 90 days. The average HbA1c decreased an absolute 0.54% in the treatment group and 0.34% in the placebo group (P=.03). Fasting blood sugar was also significantly lower in the treatment group compared with the placebo group (–9.8 vs +0.7 mg/dL; P=.02). The greatest decrease in fasting glucose was noted in patients with baseline HbA1c ≥10% (–36 mg/dL with chromium vs +16 mg/dL with placebo; P=.01).1

Evidence-Based Answer
Intratympanic gentamycin injections improve vertiginous symptoms associated with Meniere’s disease (SOR: A, consistent RCTs), although they may cause some hearing loss (SOR: B, small RCT). Also effective are oral glycopyrrolate, oral prednisone, and intratympanic injections of latanoprost or dexamethasone (SOR: B, single RCTs).

What medical treatments are effective for Meniere’s disease?

While diuretics, antihistamines, and antiemetics are commonly used treatments for Meniere’s disease, evidence is scarce to support their use. Evidence is available based on treatments of persistent vertigo.

A systematic review examined 2 RCTs comparing intratympanic injection of gentamycin with placebo in patients with Meniere’s disease uncontrolled by conservative measures. Results were reported individually. One trial (N=22) examined the effect on vertigo of an injected buffered gentamycin solution (30 mg/mL) or placebo buffer solution through the tympanic membrane every 6 weeks until symptoms were controlled or a dose of 360 mg was reached. There was a decrease in mean vertiginous attacks per year in the gentamycin group from 74 before treatment to 0 after treatment (P=.002), compared with a decrease in the placebo group from 25 to 11 (P=.028) over a follow-up period ranging from 6 to 28 months (P value for the comparison not stated).1

The other trial (N=28) used a 4-point vertigo score, with 3 corresponding to severe symptoms and 0 corresponding to no symptoms. This trial utilized a middle ear ventilation tube through which 0.4 mL of 30 mg/mL gentamycin or placebo solution was infused once per week for 4 weeks. The gentamycin group had a decrease in mean score from 2.1 to 0.5, while the placebo group’s mean score did not change significantly (from 2.0 to 1.8) over the follow-up period of 12 months. Results were reported to be significant but a P value was not provided. This study did report an average hearing loss of 8.1 dB in the gentamycin group compared with no change in the placebo group (P value not given), raising concern for cochlear toxicity.1

A RCT compared glycopyrrolate with placebo in 37 patients with Meniere’s disease and persistent vertigo despite a low-sodium diet and diuretic.

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therapy. Oral glycopyrrolate 2 mg twice a day as needed for vertigo attacks for 4 weeks decreased the mean Dizziness Handicap Inventory (DHI) score from 76, indicating severe handicap, to 37, indicating moderate handicap (P<.001), while the placebo resulted in a slight increase in mean DHI score from 73 to 75 (P=.38). Statistical analysis between groups was not given and long-term response and adverse effects were not reported.

Another RCT (N=16) compared an 18-week course of oral prednisone (0.35 mg/kg per day) plus antiemetic and diuretic with antiemetic and diuretic alone (control group) in patients with severe vertigo from Meniere’s disease. After 6 weeks, prednisone decreased the mean number of vertigo attacks per day from 1.3 to 0.50 (P<.01) and maintained this level through the 18-week treatment course, while the control group had no significant reduction in number of vertigo attacks. Follow-up at 12 months revealed 2 of 8 patients in the prednisone group had a partial relapse, and 1 had complete relapse to pretreatment levels.

A randomized crossover study (N=10) found 3 daily intratympanic injections of 10 to 20 mcg latanoprost reduced patient-reported vertigo symptoms as measured via visual analog scale by a mean of 30% compared with no change with placebo injections (P=0.039) after a 15-day follow-up. No adverse effects were reported, but the small study size does not rule out uncommon adverse effects.

Cochrane investigators reviewed the literature on intratympanic steroids compared with placebo for Meniere’s disease and identified 1 RCT of 22 patients who had previously failed medical therapy. Twenty-four months after receiving 5 daily intratympanic injections of dexamethasone or placebo (dose not stated), the dexamethasone group had significantly more patients reporting “My dizziness has no effect on my activities at all” (90% vs 42%; P<0.001) and complete control of vertigo spells (82% vs 57%; P<0.001).

In 2008, a meta-analysis examined all-cause mortality among elderly patients taking statins versus placebo for secondary prevention. It included 9 RCTs with a total of 19,569 patients aged 65 to 82 years old with known coronary artery disease. Compared with placebo, there was a reduction of all-cause mortality (RR 0.78; 95% CI, 0.65–0.89) and cardiovascular event mortality (RR 0.70; 95% CI, 0.53–0.83) in patients taking a statin.

In 2009, a meta-analysis of 10 RCTs examined the effect of statin therapy on all-cause mortality in 70,388 patients without CVD but with cardiovascular risk factors (hypertension, hyperlipidemia, smoking, and diabetes). All-cause mortality was reduced in patients taking a statin compared with placebo (RR 0.88; 95% CI, 0.81–0.96). However, once stratified by age, no significant difference was noted in all-cause mortality in patients 65 and older taking statins compared with placebo (RR 0.95; 95% CI, 0.80–1.1).

In 2010 a meta-analysis of RCTs examined the effect of statins on all-cause mortality in patients at high risk for CVD. It included 11 trials, with data from 65,229 patients (ages 51–75 years) without known CVD but at high risk for acute myocardial infarction (MI). How patients were stratified by risk was not clearly stated within this study, as the authors relied on the definitions set forth in the individual RCTs examined. There was no significant benefit of statin therapy versus placebo for all-cause mortality (RR 0.91; 95% CI, 0.83–1.01).

In 2011 a meta-analysis of 29 RCTs examined all-cause mortality among 80,711 patients at low cardiovascular risk who were taking statins versus placebo or no statins. Low cardiovascular risk was defined as those who had a risk <20% for cardiovascular-related death or nonfatal MI over 10 years as evidenced by control groups. Efforts were made to ensure that participants included did not have previous CVD. While this study did not analyze the elderly population

Do elderly patients benefit from statins?

Patients aged 65 years and older with established cardiovascular disease (CVD) benefit from HMG-CoA reductase inhibitors (statins) because they reduce all-cause mortality (SOR: A, meta-analyses). The evidence is conflicting on the mortality benefits of statin therapy in elderly patients with no known CVD.
subgroup, it did include an unknown number of patients older than 65 years and a mean age of 58 years (range, 51–76 years). The study found that all-cause mortality was lower among patients taking statins compared with placebo and no statin (RR 0.90; 95% CI, 0.84–0.97).

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Is pharmacotherapy safe and effective in the management of gallstones?

Evidence-Based Answer

In nonsurgical candidates, medical management of symptomatic cholelithiasis with ursodeoxycholic acid (UDCA) is a safe and moderately effective treatment. Success increases in patients with stones <15 mm, noncalcified stones, and a functioning gallbladder (SOR: B, small RCTs and a cohort study).

Cholecystectomy is the standard of care for patients with symptomatic cholelithiasis. Medical therapy is a valuable alternative for nonsurgical candidates. Multiple RCTs and cohort studies investigated the efficacy and safety of 2 oral treatments: chenodeoxycholic acid (CDCA), which is not currently available in the United States, and UDCA.1–3

In a double-blinded RCT, 60 individuals with cholelithiasis who were minimally symptomatic, had radiolucent gallstones, and a functioning gallbladder, were divided into treatment groups of high- or low-dose UDCA (400 vs 800 mg daily) or CDCA (375 or 750 mg daily) or placebo.1

When the dosing data were combined, UCDA showed an advantage at 12 months, with 50% dissolution rate compared with 16% and 0% of CDCA and placebo, respectively (P=.024 UDCA vs CDCA). At 24 months, the statistical significance between UCDA and CDCA disappeared, but both allowed dissolution over placebo (P value not reported). There was a statistically significant increase in elevated liver enzymes (>2 times normal) with the combined CDCA group (3 patients in the CDCA 750 group and 1 in the CDCA 375 group) compared with the combined UCDA groups (1 in the UCDA 800 group) (P=.043).1

In 1976, a double-blinded RCT of 151 asymptomatic patients with gallstones evaluated the efficacy of UDCA.2 The participants were divided into 2 dosing regimens (600 or 150 mg daily) versus placebo. The UDCA 600-mg group had a significantly higher dissolution rate at an average of 9 months compared with placebo (35% vs 5%; P<.05). There was no difference between the UDCA 150-mg group compared with placebo (17% vs 5%; P=NS). When limited to gallstones that were noncalcified and <15 mm, the dissolution rate increased to 83% in the UDCA 600-mg group compared with 17% in the placebo group (P<.05). Only 3 patients in the UCDA 600-mg group had transient transaminitis (1 in the placebo group; P>.05) and 5 had mild diarrhea (1 in the placebo group; P>.05), all of which resolved without stopping UDCA.

A prospective cohort study of 527 patients assessed if UDCA alters the clinical course of gallstone disease.3 Both symptomatic (n=74) and asymptomatic (n=107) patients were treated with UDCA 600 mg daily or placebo (n=346) and followed for an average of 81 months.

UDCA treatment resulted in a reduction of biliary pain (RR 0.19; 95% CI, 0.1–0.34) and cholecystectomy (RR 0.08; 95% CI, 0.03–0.22) in symptomatic patients compared with placebo. In asymptomatic patients, UDCA use was associated with a significant decrease in new episodes of biliary pain compared with placebo (RR 0.19; 95% CI, 0.04–0.91) but not in rates of cholecystectomy. Radiolucent stones on plain radiograph, opacification of the gallbladder, and stones <10 mm were associated with oral therapy success with hazard ratios of 13 (95% CI, 1.5–107), 11 (95% CI, 1.4–87), and 13 (95% CI, 3.4–52), respectively.3

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

Does duration of combined oral contraceptive (COC) use correlate with length of time to return to fertility?

Evidence-Based Answer
There may be an inverse correlation between the number of years of COC use and pregnancy rates the first year after discontinuation (SOR: B, retrospective cohort study). However, the average pregnancy rate at 1 year after discontinuation of COCs is similar to the rates of women who stopped barrier methods or used no contraception at all. Other issues such as increasing age may play a bigger role in delays to conception (SOR: B, observational studies).

A systematic review assessed prospective studies that reported 1-year pregnancy rates in women after cessation of reversible contraception methods. A total of 15 studies were included, and 3 of them specifically looked at 3,118 women previously taking oral contraceptives.

The average pregnancy rate 1 year after discontinuation of COCs ranged from 80% to 95% and was consistent with the rates in women who stopped barrier methods or used no contraception at all. The median number of cycles prior to conception was 2.5 to 3 versus 1.5 to 2 months in women using no contraception. Limitations of this review included heterogeneity in characteristics reported such as age, smoking, obesity, and toxin exposure. There were also no reports regarding the women’s partners, timing of intercourse, or reason for inability to conceive.

A 2002 retrospective cohort study examined 8,497 women intending to get pregnant after cessation of oral contraceptive medications. The patients and their partners were surveyed beginning at 18 weeks’ gestation to determine the time it took for the women to conceive as well as the duration of oral contraceptive use. The survey also took into account other factors such as age, education status, employment, living situation, as well as maternal and paternal alcohol and tobacco consumption, but did not ask specifics about coital frequency. Planned pregnancies reaching at least 24 weeks’ gestation were included, and of those pregnancies, time to conceive was divided into the first 6 months after cessation of oral contraceptive medications, the second 6 months, years 2 and 3, and after 3 years.

The TABLE outlines the odds ratios of conceiving in the first 12 months based on the duration of COC use. Only patients who became pregnant were studied, and there was no information gathered on the type of COC taken. Women who had been taking COCs for longer than 5 years compared with women who had been taking them for less than 1 year were more likely to conceive within 12 months (90% vs 84%; P<.001). Factors found to be statistically significant in delayed conception were older age of male and female, extremely low or high body mass index, less education, and increased exposure to tobacco smoke for the female.

<table>
<thead>
<tr>
<th>Years of COC use</th>
<th>Odds ratio of pregnancy (95% CI)</th>
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<tbody>
<tr>
<td>&gt;5 (referent)</td>
<td>1.0 (referent)</td>
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<tr>
<td>3–4</td>
<td>0.71 (0.56–0.91)</td>
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<tr>
<td>1–2</td>
<td>0.52 (0.39–0.70)</td>
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<tr>
<td>&lt;1</td>
<td>0.46 (0.33–0.65)</td>
</tr>
<tr>
<td>Never</td>
<td>0.67 (0.43–1.06)</td>
</tr>
</tbody>
</table>

*P*-value for chi² value across the Table <.001.


What is the best prophylaxis for acute mountain sickness?

Evidence-Based Answer
Ibuprofen, acetazolamide, and dexamethasone are effective in the prevention of acute mountain sickness (AMS) (SOR: B, single high-quality study and evidence-based guideline). Spironolactone and *Gingko biloba* are no better than placebo (SOR: B, individual RCTs).

In 2010, a placebo-controlled, double-blind RCT of 343 patients examined ibuprofen 600 mg TID versus acetazolamide 85 mg TID for prevention of AMS, based
on the Lake Louise questionnaire (LLQ)—a validated, Likert-scale symptom scoring system. One hundred twenty-nine patients received ibuprofen, 125 received acetazolamide, and 89 received placebo. Seventy-eight were lost to follow-up, leaving a total of 265 patients for final analysis.

Using intention-to-treat analysis, there was no difference between active agents in incidence of AMS (19% for acetazolamide vs 14% for ibuprofen; \( P = .34 \)), but both were significantly more effective than placebo (29%; \( P = .01 \)), with an NNT=8 for both. A flaw in this study is that all participants had spent several days at high altitude prior to enrollment.

A 2011 placebo-controlled, double-blind RCT of 311 patients compared spironolactone (50 mg BID, \( n = 118 \)) with acetazolamide (250 mg BID, \( n = 114 \)) and placebo (\( n = 79 \)) in AMS prevention. Thirty-five were lost to follow-up and 25 broke protocol, leaving 251 for final analysis. At 5,000 meters, using intention-to-treat analysis, 50 (20% of all participants) experienced AMS by LLQ: 13 (20%) in the placebo group, 10 (14%) in the acetazolamide group, and 27 (29%) in the spironolactone group. Spironolactone offered no significant improvement in preventing AMS when compared with placebo (\( P < .19 \)). Acetazolamide was significantly more effective in preventing AMS than spironolactone (\( P < .01 \)). A flaw in this study was that most spironolactone participants were evaluated at less than 48 hours while spironolactone’s peak effect occurs at 48 to 72 hours.

A 2005, placebo-controlled, double-blind RCT of 57 patients compared acetazolamide 250 mg BID with \( G \) biloba 120 mg BID versus placebo in the prevention of AMS. Subjects taking \( G \) biloba had no difference in AMS by LLQ when compared with placebo (65% vs 60%; \( P = .89 \)), whereas acetazolamide had a significant reduction in incidence of AMS (30% vs 60%; \( P = .01 \); NNT=3) compared with placebo.

The 2010 evidence-based guideline by the Wilderness Medical Society primarily recommends gradual ascent and acetazolamide (125 mg BID). Dexamethasone (2 mg every 6 hours or 4 mg every 12 hours) is given as an alternative for patients with a prior history of intolerance or allergic reaction to acetazolamide (Recommendation Grade 1A, “based on high-quality evidence”).


What interventions reduce the risk of contrast nephropathy for high-risk patients?

**Evidence-Based Answer**

Sodium bicarbonate and high-dose N-acetylcysteine are effective in preventing contrast-induced nephropathy. Saline hydration alone is less effective than sodium bicarbonate. Statins do not appear to be effective (SOR: A, meta-analyses).

A meta-analysis of 10 RCTs including 1,090 patients with some degree of renal insufficiency at baseline compared the occurrence of contrast-induced nephropathy (CIN) after pretreatment with sodium bicarbonate or sodium chloride. The concentrations and rates of intravenous (IV) infusion varied. Most studies defined CIN as a relative increase in creatinine of >25% or an absolute increase in creatinine of >0.5 mg/dL. Most of the subjects were undergoing cardiac angiography with a nonionic low osmolar contrast agent.

There was a significant decrease in the development of CIN in the sodium bicarbonate group compared with the sodium chloride group (OR 0.57; 95% CI, 0.38–0.85). The meta-analysis had no evidence of heterogeneity or publication bias.

A meta-analysis of 16 RCTs including 1,677 patients evaluated the role of high-dose N-acetylcysteine for the prevention of CIN. Most of these patients had some renal insufficiency, with a weighted mean serum creatinine concentration of 1.58 mg/dL. High dose was defined as a daily dose of N-acetylcysteine >1,200 mg or a single periprocedural dose >600 mg, given immediately or within 4 hours of the planned contrast exposure. The contrast agents used varied.

There was significant decrease in the occurrence of CIN in the N-acetylcysteine group compared with placebo (OR 0.46; 95% CI, 0.33–0.63). The meta-
A meta-analysis evaluated the effects of statins on the incidence of CIN in patients undergoing coronary angiography. Three RCTs involving 770 patients and 7 nonrandomized trials involving nearly 32,000 patients were studied. In 4 trials, including the 3 RCTS, statin therapy was administered to 1,683 patients acutely for 1 to 2 days before and after coronary angiography. In the remaining studies, the patients were already on chronic statin therapy. Although the quality of 2 of the RCTs was judged to be excellent, the quality of the remainder of the studies was assessed as poor.

The RCTs of statin therapy did not show significant benefit (OR 0.76; 95% CI, 0.41–1.4; P=.39). No significant heterogeneity was found in the RCTs. The nonrandomized studies showed a marginally significant benefit of statins (OR 0.60; 95% CI, 0.36–1.0; P=.05). There was significant heterogeneity among the nonrandomized studies.

A meta-analysis performed on 13 studies of primarily SSRIs (N=1,272) demonstrated a greater responder rate to treatment with medication for an average of 11 weeks compared with placebo, as measured by the Clinical Global Impressions scale or similar instrument (59% vs 39%; RR 1.5; 95% CI, 1.3–1.7; NNT=5). Paroxetine (RR 1.6; 95% CI, 1.4–2.0) and sertraline (RR 1.7; 95% CI, 1.2–2.4) showed the greatest benefit. Medications also resulted in a significant reduction in symptoms scores on the Clinician-Administered PTSD Scale (CAPS; a validated scale for measuring PTSD symptoms from 1 to 100) compared with placebo (17 trials; N=2,507; weighted mean difference −5.8; 95% CI, −8.2 to −3.4). The authors concluded that SSRIs are reasonable first-line pharmacotherapy agents for PTSD.

A 2010 Clinical Evidence review examined multiple treatment options for PTSD, including antidepressants. It included a systematic review of 3 RCTs (N=1,070) that demonstrated paroxetine more effective than placebo for reducing the severity of PTSD symptoms using the CAPS scale (standard mean difference [SMD] −0.42; 95% CI, −0.55 to −0.30). Another systematic review of 2 RCTs (N=499) evaluated 8 to 12 weeks of fluoxetine compared with placebo. There was no significant difference in symptom reduction between groups. The review authors noted that the withdrawal rate and the effects of other interventions in these studies were unclear, making this evidence of lower quality. An RCT discussed in the review (N=301) compared 20 to 40 mg fluoxetine with placebo and favored fluoxetine using the CAPS score (SMD −0.28; 95% CI, −0.54 to −0.02). However, absolute results were not reported and the evidence was again determined to be of low quality.

A 2005 National Institute for Health and Clinical Excellence (NICE) guideline evaluated 26 RCTs of drug treatment versus placebo on numerous outcomes. Fifteen of the RCTs studied an SSRI versus placebo (4 paroxetine, 6 sertraline, and 5 fluoxetine). Meta-analyses of each SSRI included 625 patients taking paroxetine, 559 taking sertraline, and 549 taking fluoxetine.

All 3 meta-analyses showed symptom reduction on the CAPS in patients taking SARI versus placebo. However, the effects of paroxetine (SMD −0.42;
95% CI, –0.55 to –0.22), sertraline (SMD –0.26; 95% CI, –0.51 to –0.00), and fluoxetine (SMD –0.11; 95% CI, –0.29 to –0.06) were all less than the pre-analysis assumption of a SMD of less than –0.5 being clinically significant.³

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When and how should functional hypothalamic amenorrhea in female athletes be treated?

**Evidence-Based Answer**

Oral contraceptive pill (OCP) use in women runners with oligomenorrhea or amenorrhea is associated with increased bone mineral density (BMD), but no decrease in stress fracture incidence (SOR: B, single RCT). Decreased training, increased caloric intake, and weight gain predict spontaneous resumption of menses (SOR: A, evidence-based guideline).

A 2007 unblinded RCT investigated the effects of OCP use on bone mass and stress fracture incidence in 150 female distance runners (aged 18–26 years).¹ Researchers randomly assigned participants to receive either OCP treatment (30 mcg ethinyl estradiol and 0.3 mg norgestrel) or no treatment over 2 years. BMD and bone mineral content (BMC) were measured using DEXA scans at baseline, year 1, and year 2.

Women with oligo/amenorrhea who took OCPs did not have a decreased risk of fracture (HR 0.60; 95% CI, 0.06–5.8) compared with oligo/amenorrhea patients on no treatment and there was no decrease in fracture risk in eumenorrheic patients on OCP compared with eumenorrheic patients on no treatment (HR 0.56; 95% CI, 0.14–2.2). Compared with women who remained oligo/amenorrheic not taking OCPs, OCP users who regained menses gained significantly more whole-body BMC (2% with OCPs vs –1% oligo without OCPs; P<.05) and spine BMD (2% with OCPs vs 0% oligo without OCPs; P<.05).¹

The American College of Sports Medicine, in preparing its 2007 position statement, evaluated the available evidence on the female athlete triad.² The authors found “consistent, good quality evidence” on morbidity, mortality, symptom improvement, cost reduction, and quality of life supporting the following statements:

1. Severe undernutrition impairs reproductive and skeletal health.
2. Disordered eating/eating disorders (DE/ED) and amenorrhea occur more frequently in sports that emphasize leanness.
3. Menstrual irregularities and low BMD increase stress fracture risk.

The authors also found “inconsistent or limited quality evidence” supporting these statements:

1. To diagnose functional hypothalamic amenorrhea (FHA), other causes of amenorrhea must be excluded.
2. Treatment for DE/ED includes nutritional counseling and individual psychotherapy or group and/or family therapy. When any of the above symptoms (menstrual irregularities, disordered eating, or severe undernutrition) are present, investigation and treatment should be initiated.

Based on “case studies, usual practice, consensus, and opinion,” the guidelines also stated that (1) treatment should be aimed at eating more and/or exercising less, since weight gain is often sufficient for resumption of menses; (2) athletes without disordered eating should be referred for nutritional counseling; and (3) patients older than 16 with FHA should be considered candidates for treatment with OCPs if the patient has decreasing BMD with nonpharmacological management, despite adequate nutrition and body weight.² The authors did not identify any pharmacological agent that could reverse bone loss or correct the metabolic abnormalities associated with FHA.

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Are NSAIDs harmful in the acute healing of fractures?

**Evidence-Based Answer**
NSAIDs do not increase the risk of nonunion if used for a short period (up to 8 weeks) of time (SOR: B, cohort studies and small RCTs.) There is an association between long-term (>60 days) NSAID use and nonunion of fractures, but whether this relationship is causal is less clear.

In 2005, a cohort trial of 9,995 patients with humeral shaft fractures evaluated the effects of NSAIDs and nonunion of fractures. From a Medicare database, authors were able to identify how many patients had nonunions (105 or 1.1%) and how many patients had NSAID exposure within 90 days after the fracture (1,032 or 10.3%).

Only exposure during the period of 61 to 90 days postfracture showed a significant association between NSAID use and nonunion (RR 3.9%; 95% CI, 2.0–6.2). There was a similar association between opioid use and nonunion at the same 61- to 90-day postfracture time frame, but not in the preceding 60 days. The conclusion was that the association of NSAIDs with nonunion may be causal, but it more likely reflects the extended use of pain medications to cope with nonhealing fractures.

A case-control trial in the United Kingdom from 2000 evaluated 99 patients who underwent intermedullary nailing of femoral shaft fractures and the effects of NSAIDs on bone healing. Thirty-two patients had a nonunion while 67 had successful bone healing. There was a significant difference in the use of NSAIDs between the nonunion (63%) and the healing group (13%) (P <0.001). The nonunion group tended to use NSAIDs for much longer (21 vs 1 week). The authors concluded that this demonstrated a causal relationship between NSAIDs and nonunion, although again reverse causation is possible.

In 1993, a small prospective RCT of 42 postmenopausal women with a first Colles’ fracture was performed to evaluate the effects of NSAIDs on bone healing. Women were given piroxicam 20 mg daily or placebo. Outcomes were measured by functional recovery and radiological changes. There was no difference in recovery rates at 12 weeks. The weakness of this study is that it was a small study and had short follow-up.

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What is the best approach to anhidrosis (absence of sweating) in an otherwise healthy adult?

**Evidence-Based Answer**
Acquired idiopathic generalized anhidrosis (AIGA) may be treated with intravenous (IV) methylprednisolone 1,000 mg for 3 days. Identification and management of secondary causes is essential, and medications known to cause anhidrosis should be discontinued (SOR: C, case series).

Primary AIGA is extremely rare and the cause is unknown. A case series of 8 patients (14–30 years old) found pilocarpine-induced sweat testing abnormal in all; quantitative emotional sweat testing was normal in the 4 in which it was performed; and microneurographic analysis of skin sympathetic nerve activity done in 2 patients was normal in 1 and hyperactive in 1. Three cases recovered spontaneously. IV methylprednisolone, 500 to 1,000 mg daily for 3 days resulted in successful treatment (defined as improved sweating or normal thermoregulatory sweating at 2 months and resolution of pain or discomfort) in the remaining 5 patients.

A case report involved a 39-year-old man who complained of a 6-month history of heat intolerance, lack of sweating with tachycardia, and fatigue. A diagnosis of AIGA was made by the pilocarpine-induced sweat test, thermoregulatory testing, and a skin biopsy revealing lymphocytic infiltration of sweat glands. The patient was treated with IV methylprednisolone 1,000 mg daily for 3 days followed by a 2-week taper of oral doses (dose not specified), which resulted in improved sweat production at 1 week, and normalized thermoregulatory testing and skin biopsy at 2 months.
Another case report reviewed a single patient diagnosed with AIGA by an abnormal starch iodine test, abnormal pilocarpine, norepinephrine, and epinephrine injections sweat studies, and lymphocytic infiltration around sweat glands on skin biopsy. The patient was treated successfully (defined as resolution of symptoms and clearing of skin biopsy findings) with daily methylprednisolone 1,000 mg IV for 3 days followed by a taper (60 mg prednisolone daily for 2 weeks followed by a dose reduction of 10 mg every other week).

Secondary causes of hypohidrosis and anhidrosis include Parkinson’s disease, progressive supranuclear palsy, pallido-ponto-nigral degeneration, multiple sclerosis, stroke, spinal cord transection, Fabry disease, diabetes mellitus, Sjögren’s disease, acute pandysautonomia, familial amyloidotic polyneuropathy, Ross syndrome, thyroid dysfunction, congenital absence of sweat glands, and medications.

Treatment of the underlying disorder or discontinuing medications (TABLE) is recommended.

### Medications causing hypohydrosis

<table>
<thead>
<tr>
<th></th>
<th>Diphenhydramine</th>
<th>Doxepin</th>
<th>Promethazine</th>
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<tr>
<td>Amitriptyline</td>
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<td>Atropine</td>
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<td>Belladonna</td>
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<td>Botulinum toxins</td>
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<td>Carbamazepine</td>
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<td>Desipramine</td>
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<td>Quetiapine</td>
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<td>Solifenacin</td>
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<td>Thioridazine</td>
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<td>Zonisamide</td>
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A RCT (N=161) evaluated a 10-day course of trimethoprim/sulfamethoxazole (trim/sulfa) compared with placebo after abscess I&D in children (aged 3 months to 18 years). Patients were seen in the emergency department, were nontoxic appearing, and had temperatures of less than 38.4°C. Patients with diabetes, immune suppression, or recent antibiotic use were excluded.

Clinical failure (presence of erythema, warmth, induration, fluctuance, tenderness, or drainage at 10 days) was similar between the trim/sulfa and placebo arms (4.1% vs 5.3% in placebo arm with an absolute difference of 1.2%; 1-sided 95% CI, –∞ to 6.8%, where noninferiority is assumed if the upper limit of the CI is <7%). The trim/sulfa group did have fewer new lesions at the 10-day follow-up (13% vs 26%, with an absolute difference of 14%; 1-sided 95% CI, –∞ to 24%). Limitations included possible selection bias and incomplete appointment follow-up resulting in 40% being done by phone.

A multicenter RCT (N=212) compared a 7-day course of trim/sulfa with placebo after abscess I&D in adults with uncomplicated skin abscesses. Patients who were immune-compromised, ill, or had complicated abscesses (face location, tracts/fistulas to deeper structures, abscesses requiring operating room drainage) were excluded.

Treatment failures within 7 days (defined as no improvement in 2 days, new lesions or worsening infection within 7 days, or additional intervention required) were similar between the trim/sulfa and placebo groups (17% vs 26%; 95% CI for difference, –2 to 21). The trim/sulfa group did have fewer new lesions at the 30-day follow-up (9% vs 28%; 95% CI for difference, 4–34). Limitations included only 69% follow-up at 30 days and the possibility that medicaments causing hypohydrosis remain unknown.

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results may not generalize to children or patients with comorbidities.\(^2\)

A RCT (N=166) compared a 7-day course of cephalexin 500 mg BID with placebo after abscess I&O in urban outpatient adults with a history of intravenous drug use, hepatitis B, hepatitis C, HIV, diabetes, and fever.\(^3\) The trial excluded patients with complicated abscesses or who appeared more ill.

The proportion of patients with clinical cure (no drainage, erythema, fluctuance, warmth, pain/tenderness, edema/induration, or additional treatment required) was similar between the groups at 7 days (84% vs 90.5%; \(P>.05\)). Culture results isolated *Staphylococcus aureus* in 67% of both groups; 88% of those were MRSA. Limitations included using an antibiotic with no activity against MRSA, adherence based on self-report, no evaluation of recurrence, and the question of generalizability given the unique population studied.\(^3\)

The Infectious Diseases Society of America evidence-based guideline recommends antibiotics for abscess treatment in the setting of severe/extensive disease, rapid progression of cellulitis, systemic illness, comorbidities or immune suppression (diabetes, HIV/AIDS, neoplasm), extremes of age, locations difficult to drain, association with septic phlebitis, or when there is lack of response to I&O alone (recommendation based on good-quality evidence).\(^4\)

**Does cough in patients with miliary tuberculosis increase contagion risk?**

Evidence-Based Answer

It seems likely. While there are no studies directly addressing the infectivity of miliary tuberculosis (TB), 89%–95% of patients with miliary TB have radiographic findings of pulmonary disease, 36%–76% have positive sputum positive acid-fast bacilli (AFB) smears or culture, and 37%–82% have cough on presentation (SOR: C, extrapolated from case studies).

TB is nearly always transmitted by inhalation of bacteria within aerosolized particles, typically from sputum produced by coughing, singing, and sneezing. Increased infectivity is associated with prolonged, confined, and concentrated exposure to symptomatic patients. The highest rate of transmission occurs in patients with positive AFB smears or cavitary lesions on chest x-ray. Miliary TB describes a rare form of TB with massive lymphatic and hematologic dissemination during primary or reactivated infection, uniformly fatal if untreated.\(^1,2\)

A comprehensive review of 21 hospital-based case series and autopsy studies from 1950 to 2004 evaluated the risk factors, clinical features, diagnostic studies, treatment, and mortality associated with miliary TB.\(^1\) There were no studies evaluating transmission of *Mycobacterium tuberculosis* from patients with miliary TB. Most patients presented with cough/sputum production (37%–82%).

In a 2001 case series from a Turkish hospital with miliary TB diagnosed by chest x-ray, high-resolution CT, biopsy, or autopsy of 38 adults with unknown HIV status, cough was a presenting complaint in 68% of patients, pulmonary abnormalities were noted on 92% of chest x-rays, and granulomata were found in 85% of lung biopsies.\(^3\)

Another case series of 38 patients without AIDS discharged from a university hospital and VA hospital with culture-confirmed miliary TB showed cough at presentation in 55% of patients, chest x-rays suggestive of pulmonary disease in 89% of patients, positive sputum smears positive in 12 of 33 (36%) patients tested, and sputum culture positive in 25 of 33 (76%) patients tested.\(^4\)

A 2004 case series describing patients diagnosed with miliary TB admitted to a university hospital in
Karachi, Pakistan between 1994 and 2001. Criteria for the diagnosis of miliary TB required multiorgan involvement or miliary pattern on chest x-ray and clinical features, positive smear or culture, or histopathological evidence of TB. Only 41% of patients exhibited cough; however, 96% had abnormal chest x-rays. AFB smear was positive in 8 of 22 sputum samples and 2 of 5 transbronchial biopsy specimens, while culture was positive in 12 of 22 sputum samples and 2 of 5 transbronchial biopsy specimens.

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Is acetaminophen as effective as NSAIDs for pain relief in acute ankle sprains?

Evidence-Based Answer
Yes. Acetaminophen improves pain and function just as well if not better than nonsteroidal anti-inflammatory drugs (NSAIDs) in acute ankle sprains (SOR: B, heterogeneous RCTs).

A RCT compared effectiveness of a 10-day course of acetaminophen 500 mg 3 times daily with diclofenac 75 mg twice daily in 90 patients aged 18 to 60 with acute type II ankle sprains. Reduction in pain on days 3 and 10 were compared. Pain was assessed using a 100-point visual analog scale (VAS) with weight bearing. At baseline, VAS scores for the acetaminophen and diclofenac group were 73 and 70, respectively (not statistically significant). Likewise, there was no difference in mean pain scores between patients treated with acetaminophen or diclofenac on day 3 (22 vs 22, respectively; P=.9) or day 10 (5.1 vs 6.9; P=.3).

Another RCT compared the effectiveness of acetaminophen 500 mg 3 times daily with diclofenac 75 mg twice daily for 5 days in 100 patients, 18 years and older, with grade I or II acute ankle sprains. Pain scores, using the 100-point VAS, were assessed at baseline, on days 2 and 10, and at 6 weeks. The initial mean VAS scores were similar in the acetaminophen and diclofenac groups (82 and 81, respectively; P=.51). Mean pain scores were better with acetaminophen than diclofenac at day 2 (12 vs 21; P=.001) and day 10 (8.3 vs 9.9; P=.02), but were similar at 6 weeks (3 vs 4.6; P=.19).

How effective is hypnosis for chronic pain?

Evidence-Based Answer
Hypnosis produces a significant decrease in the pain associated with a variety of chronic pain problems. The effects can be maintained for months (SOR: B, systematic reviews of RCTs without assessment of study quality).

A systematic review of 11 studies with a variety of designs (6 RCTs with unclear blinding, 2 RCTs with blinding, 2 cohort trials with unclear blinding, 1 case series; N=769) examined the effectiveness of hypnosis for the treatment of headaches and migraines. The techniques used were hypnotically facilitated relaxation and imagery combined with encouraging the daily practice of self-hypnosis, often with a self-hypnosis tape. The sample size per trial varied from 11 to 260 subjects. The authors of this systematic review did not attempt to combine the study results, but all studies reviewed showed some benefit. Overall, the reviewers concluded that hypnosis is superior or equivalent to commonly used medications. The search methodology
was not described, nor did the author evaluate the quality of the studies.

Another review described 13 RCTs (blinding not specified) of hypnosis for the treatment of chronic pain in a total of 447 patients from the following causes: cancer (2 trials), low-back problems (2 trials), arthritis, sickle-cell disease, or temporomandibular conditions (2 trials), fibromyalgia, physical disability, and mixed etiologies (3 trials). The duration of hypnosis treatment varied from 4 weeks to 18 months. All the studies were small (17–54 subjects) and heterogeneity of protocol precluded a meta-analysis.

In all of the studies, hypnosis was significantly more effective than no treatment or interventions such as physical therapy in reducing pain. In some cases, the pain reduction was maintained for several months. The search methodology was not described, nor did the authors evaluate the quality of the studies.

A review of 4 recent RCTs (116 patients) evaluated the efficacy of self-hypnosis for management of chronic pain from a variety of causes. The studies included the step of making audio recordings of treatment sessions and using them for practicing self-hypnosis at home. Outcomes were not combined. The results included a decrease in chronic daily pain that was maintained for up to a year in a subset of patients with disabilities.

**Which triptan is most effective for acute migraine therapy?**

Evidence-Based Answer

Oral eletriptan and rizatriptan appear to be more likely than oral sumatriptan to achieve a pain-free response at 2 hours for moderate to severe migraines. All triptans were more effective than placebo at relieving pain at 2 hours (SOR: A, systematic review of RCTs).

A 2012 Cochrane review of 61 RCTs involving 37,250 participants evaluated the effectiveness of oral sumatriptan for the treatment of acute migraine. For patients with moderate to severe pain at baseline (scores of 2 or 3 on a scale of 0–3), oral sumatriptan 100 mg was more likely than placebo to achieve a pain-free response at 2 hours (16 trials, N = 6,571; risk ratio [RR] 3.2; 95% CI, 2.8–3.6; NNT=4). In direct comparator trials, oral sumatriptan 100 mg was less likely than oral eletriptan 80 mg to achieve a pain-free response at 2 hours (2 trials, N=604; RR 0.5; 95% CI, 0.4–0.7; NNT with eletriptan=7). Oral sumatriptan 100 mg was also less likely than oral rizatriptan 10 mg to eliminate pain at 2 hours (2 trials, N=936; RR 0.8; 95% CI, 0.6–0.9; NNT with rizatriptan=16).

A separate 2012 Cochrane review evaluated the effectiveness of subcutaneous sumatriptan in the treatment of moderate to severe migraine headache pain. Most trials evaluated the 6-mg dose. Subcutaneous sumatriptan 6 mg was more likely than placebo to achieve a pain-free response at 2 hours (13 trials, N=2,522; RR 3.8; 95% CI, 3.3–4.4; NNT=2).

A 2002 systematic review of 54 RCTs involving 21,022 participants evaluated the effectiveness of multiple therapies for the treatment of acute migraine. Five triptans—including intranasal, oral, and subcutaneous sumatriptan—were included, and authors compared each medication’s performance versus placebo. All triptans were more effective than placebo at eliminating moderate to severe migraine headache pain at 2 hours (TABLE).

**TABLE**

<table>
<thead>
<tr>
<th>Medication and dose</th>
<th># Trials (participants)</th>
<th>RR (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eletriptan 80 mg PO</td>
<td>6 (2,000)</td>
<td>6.4 (4.6–8.9)</td>
<td>4</td>
</tr>
<tr>
<td>Naratriptan 2.5 mg PO</td>
<td>1 (320)</td>
<td>2.5 (1.3–4.8)</td>
<td>8</td>
</tr>
<tr>
<td>Rizatriptan 10 mg PO</td>
<td>7 (2,770)</td>
<td>4.8 (3.8–5.9)</td>
<td>3</td>
</tr>
<tr>
<td>Sumatriptan 20 mg INH</td>
<td>3 (812)</td>
<td>2.9 (2.0–4.0)</td>
<td>5</td>
</tr>
<tr>
<td>Sumatriptan 100 mg PO</td>
<td>8 (2,205)</td>
<td>3.6 (2.8–5.5)</td>
<td>5</td>
</tr>
<tr>
<td>Sumatriptan 6 mg SQ</td>
<td>6 (683)</td>
<td>4.4 (3.2–6.0)</td>
<td>2</td>
</tr>
<tr>
<td>Zolmitriptan 5 mg PO</td>
<td>4 (1,228)</td>
<td>5.1 (3.3–8.1)</td>
<td>4</td>
</tr>
</tbody>
</table>


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What are good combinations of antidepressants if the first one does not work?

Evidence-Based Answer
Switching to mirtazapine or adding bupropion may increase response rates in patients with depression who do not respond adequately to selective serotonin reuptake inhibitor (SSRI) monotherapy (SOR: B, small randomized trials).

A double-blind RCT of 26 patients (3 with bipolar II and 23 with unipolar depression) examined the effectiveness of adding mirtazapine (15–45 mg daily) compared with placebo in patients who failed monotherapy with an SSRI, bupropion, or venlafaxine.¹ Compared with the placebo group after 4 weeks, patients in the mirtazapine group had a significantly greater response, measured with the Clinical Global Impression-Improvement score (64% vs 20%; \( P=.04 \)) and by a 50% reduction in the Hamilton Rating Scale for Depression (64% vs 20%; \( P=.04 \)). The remission rate (a HRSD-17 score <8 by the end of the trial) was not significantly different (45% vs 13%; \( P=.068 \)) between mirtazapine and placebo.

A RCT examined the effectiveness of adding bupropion-extended release (279 patients, 400 mg/d) or buspirone (286 patients, 60 mg/d) to citalopram (60 mg/d) in patients with nonpsychotic major depressive disorder who failed to improve with citalopram alone.² The primary outcome was a score <8 on the HRSD-17. Rates of response (defined as a reduction of ≥50% from the baseline Quick Inventory of Depression Symptomatology-Self Report-16) and a QIDS-SR score <6 were secondary outcomes. There was no difference after 12 weeks for remissions rates with bupropion (30%) and buspirone (30%) (\( P=.93 \)). However, the bupropion group demonstrated a greater response rate with the QIDS-SR-16 than the buspirone group (25% vs 17%; \( P<.04 \)) and lower withdrawal from the study due to adverse effects (13% vs 21%; \( P<.009 \)).

A RCT evaluated venlafaxine (300 mg/d) plus mirtazapine (45 mg/d) versus the MAO inhibitor tranylcypromine (60 mg/d) alone in 109 patients with nonpsychotic major depressive disorder who had failed monotherapy with citalopram and subsequent attempts of augmentation, combination, or change of their monotherapy class.³ Remission was defined as a score <6 on the Quick Inventory of Depression Symptomatology (QIDS-C-16) and a score of <8 on the Hamilton Depression Rating Scale. After 12 weeks, there was no difference in the achievement of remission with tranylcypromine (58 patients, 14%) compared with venlafaxine plus mirtazapine (51 patients, 16%) (\( P=.9 \)).

Do certain support surfaces reduce the risk of pressure ulcers more than others?

Evidence-Based Answer
Foam surfaces and sheepskin overlays are superior to standard hospital mattresses (SHM) for overall pressure ulcer prevention. There is no significant difference in pressure ulcer prevention with alternating pressure (AP) surfaces compared with constant low-pressure (CLP) surfaces. Use of a Micropulse® AP overlay system with a gel pad during surgery and continued after surgery reduces pressure ulcer incidence compared with a SHM postoperatively (SOR: A, meta-analyses of RCTs). Foam and air-supported surfaces also significantly reduce heel ulcer incidence compared with SHMs, while foam boots do not (SOR: B, meta-analyses of limited-quality RCTs).

A Cochrane review of 53 RCTs evaluated a variety of support surfaces for prevention of pressure ulcers.¹ Foam alternatives were superior to SHM for reducing incidence of pressure ulcers in at-risk (primarily orthopedic, oncology, or general medical ward) hospitalized patients (5 trials, \( N=2,016 \); RR 0.40; 95% CI, 0.21–0.74; \( P=.004 \)). Australian medical sheepskin overlays were also more effective than SHMs for reducing the incidence of all grades of pressure ulcers (including grade 1) in both orthopedic and aged-care facility patients (3 trials, \( N=1,281 \); RR 0.48; 95% CI, 0.31–0.74; \( P=.004 \)).

AP supports were no different form CLP surfaces (overlays, foam pads, and water-, air-, and visco-elastic foam mattresses) in pressure ulcer incidence in hospital inpatient (orthopedic, medical-surgical, and neurological wards) and aged-care facility residents (9 trials, \( N=1,376 \); RR 0.85; 95% CI, 0.64–1.13; \( P=.28 \)). A Micropulse AP system (used both during

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surgery and postoperatively) with a gel pad during surgery decreased pressure ulcer risk compared with SHM postoperatively (2 trials, N=368; RR 0.21; 95% CI, 0.06–0.7; \( P=0.11 \)). A single RCT compared using a visco-elastic overlay pad on a standard operating table (n=205) with no pad (n=211) for patient >55 years undergoing surgery in supine or lithotomy position. A 47% reduction in incidence of postoperative pressure ulcers was associated with use of the polymer overlay pad (RR 0.53; 95% CI, 0.33–0.85; \( P=0.008 \)).

A meta-analysis of 14 RCTs (N=1,457, mean age 76 years) evaluated the effect of pressure-relieving surfaces on prevention of heel ulcers. Foam mattresses were more effective than SHM in reducing the number of heel ulcers in acute and long-term care settings (3 trials, N=241; RR 0.40; 95% CI, 0.16–0.99; \( P=0.05 \)). Overall, pressure-reducing surfaces (air or foam mattresses or overlays) were associated with a significantly lower incidence of heel ulcers compared with SHM (8 trials, N=798; RR 0.50; 95% CI, 0.26–0.93; \( P=0.03 \)). There was no difference in the incidence of heel ulcers with use of heel protective devices compared with standard hospital pillow (2 trials; N=216; RR 0.33, 95% CI, 0.01–7.82; \( P=0.50 \)).


How commonly does initiation of allopurinol for hyperuricemia trigger a gout flare?

Evidence-Based Answer

Without the use of prophylactic colchicine, roughly three-quarters of patients experience a gout flare in the first 6 months of starting allopurinol. Colchicine reduces the risk by approximately half (SOR: B, RCTs).

A RCT (N=43) of patients with gout in a rheumatology practice compared prophylaxis with colchicine 0.6 mg daily (n=21) vs placebo (n=22) upon initiation of allopurinol. The baseline uric acid level was 9.5 mg/dL in the treatment versus 9.2 mg/dL in the placebo group (no \( P \) value provided). Allopurinol starting at 100 mg daily was titrated up monthly to decrease the uric acid level <6.5 mg/dL. Patients were followed for 3 months after achieving targeted uric acid levels, evaluating patient-reported gout flares.

In 6 months of follow-up, prophylaxis with colchicine reduced the incidence of gout flares compared with placebo (33% vs 77%; \( P=0.008 \)).

A retrospective study examined 267 patients started on uric acid–lowering therapy (n=232) (allopurinol up to 300 mg or benzbromarone up to 50 mg) compared with 35 patients who did not start uric acid–lowering therapy and followed them for more than 3 years.

With no use of prophylactic anti-inflammatory drug or colchicine, there was a 1.5- to 2-fold increase in gout attacks in the first 6 months among patients on uric acid–lowering therapy (interpretation of graphed data, no OR). However, over the entire 3-year period, use of an anti-hyperuricemic drug decreased the risk of recurrent gout attacks compared with no drug (30% vs 63%; \( P<0.001 \); OR 0.22; 95% CI, 0.10–0.47; NNT=3).

Two RCTs that combined data evaluated 1,832 patients with gout and a baseline uric acid of ≥8 mg/dL, comparing allopurinol 300 mg (N=251), febuxostat 80 mg (N=257), febuxostat 120 mg (N=251), or placebo (N=1,072) daily for reducing recurrent gout attacks. All subjects received colchicine 0.6 mg daily or naproxen 250 mg daily for prophylaxis during the first 8 weeks of therapy. Approximately 20% of individuals in all groups experienced a flare within 4 weeks of initiation of active medication or placebo while on prophylaxis. There was an increased incidence of flare during the 4-week period after removal of prophylaxis (weeks 9–12) among those treated with allopurinol or febuxostat and serum urate levels reduced to <6 mg/dL compared with patients whose uric acid level remained >6 mg/dL and receiving either treatment or placebo (42% vs 28%; \( P<0.001 \)). Long term, the risk of flare was significantly less in individuals with serum urate levels <6.0 mg/dL at 52 weeks after initiation of therapy compared with individuals with serum urate levels >6.0 mg/dL, regardless of treatment arm (4% vs 18%; \( P=0.002 \)).