What is the best treatment for plant-induced contact dermatitis?

Evidence-based answer

It is unclear which treatment is best, because there have been no head-to-head comparisons of treatments for Rhus (plant-induced) contact dermatitis. That said, topical high-potency steroids slightly improve pruritus and the appearance of the rash (strength of recommendation [SOR]: B, small cohort studies).

Neither topical pimecrolimus (an immunomodulatory drug) nor jewelweed extract are helpful (SOR: B, 1 small randomized controlled trial [RCT]).

Oral steroids improve symptoms in severe cases (SOR: C, expert opinion).

Evidence summary

Two prospective, self-controlled cohort studies (N=30) showed that high-potency topical steroids improved symptoms associated with artificially induced Rhus dermatitis in a group with a history of that type of dermatitis.1,2

The first study found that 0.05% clobetasol propionate ointment applied twice a day significantly reduced overall vesiculation, erythema, induration, and pruritus compared with the control (P<0.05, 0.01, 0.01, and 0.05, respectively).1 Investigators evaluated erythema, induration, and pruritus on a scale of 0 to 3 (absent, mild, moderate, or severe) and graded vesiculation on a similar 0-to-3-point scale (a frank bulla was graded 3). They started treatment at 12, 24, and 48 hours after exposure and followed patients for 14 days. The greatest difference in mean scores—a reduction in vesiculation scores of approximately 1 point—occurred between 2 and 7 days of therapy.

The second study compared improvement in symptoms of Rhus dermatitis with daily application of topical steroids of different potencies and a control ointment.2 Investigators evaluated healing using a 0-to-4-point scale (0=clearing and 4=marked edema,
erythema, and vesiculation). They found that lower-potency topical steroids such as 1% hydrocortisone and 0.1% triamcinolone were equivalent to the control ointment, but high-potency (class IV) steroid ointments produced significant improvement in symptoms (by a mean of 1.07 points vs the control ointment; supporting statistics not given).

A systematic review of contact dermatitis treatment and prevention identified 4 “good-quality” RCTs that evaluated effective remedies for nickel-induced allergic contact dermatitis in a predominantly female Caucasian population. All found that moderately high-potency topical steroid therapy improved symptoms, but heterogeneity among the studies made it impossible to determine the best agent.

Topical immunomodulatory drugs and jewelweed are no help

In a double-blinded RCT of 12 adults with a history of Rhus dermatitis and a significant reaction to tincture of poison ivy, topical pimecrolimus did not improve the duration or severity of symptoms \((P\text{-value: nonsignificant})\).

A similar RCT from a dermatology clinic of 10 adults with confirmed sensitivity to poison oak or ivy found that topical jewelweed extract did not improve symptoms of artificially induced Rhus dermatitis. Investigators did not report \(P\) values.

Oral steroids have not been studied

No studies have evaluated the effectiveness of oral steroids for Rhus dermatitis. Expert opinion recommends prednisone (60 mg daily, tapered over 14 days) for severe and widespread cases of poison ivy dermatitis.

Recommendations

The American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology jointly recommend topical corticosteroids as first-line treatment for localized allergic contact dermatitis. They advise giving systemic corticosteroids for lesions covering more than 20% of body surface area (for example, prednisone 0.5–1 mg/kg per day for 5–7 days, then 50% of the dose for another 5–7 days).

The American Academy of Dermatology has not issued guidelines on plant-induced dermatitis. A dermatology textbook states that topical steroids are effective during the early stages of an outbreak, when vesicles and blisters are not yet present, and that systemic steroids are extremely effective for severe outbreaks. The authors recommend treating weepy lesions with tepid baths, wet to dry soaks, or calamine lotion to dry the lesions.

Evidence-Based Practice learning objectives

1. To become knowledgeable about evidence-based solutions to commonly encountered clinical problems.
2. To understand how ground-breaking research is changing the practice of family medicine.
3. To become conversant with balanced appraisals of drugs that are marketed to physicians and consumers.
From the Editor

Reason and reversal

Dear EBP Readers,

A couple of hiking buddies and I climbed Mount St. Helens a few years back. We made it to the summit, but afterwards we all agreed that it was the most gosh-awful hiking any of us had ever endured. As the adventure unfolded, somehow we managed to miss plenty of good opportunities to turn around, like when

- Half the party did not even bother to show up at the trailhead
- It started to rain
- It started to snow
- Mike’s lips turned blue
- Whiteout conditions developed
- Laura could no longer see clearly when her glasses froze over

It just goes to show that sometimes we get so intent on our destination that we miss solid evidence that the best option would be to stop and turn around. This is as true for slightly dysfunctional climbing teams (Mike and Laura know what I mean) as it is for the practice of medicine.

Not infrequently, the medical system will launch off in a particular direction, only to have to completely reverse course some time later. Some wayward practices—estrogen replacement for all postmenopausal women or use of class Ic antiarrhythmics to name just 2—were abandoned relatively quickly. Other practices have been harder to dislodge, such as vertebroplasty for compression fractures and stents for stable coronary artery disease. What? You’re still doing these? That just makes a further point: once an industry builds up around an idea, evidence becomes politicized and good research may be lost in a blizzard of opinion pieces.

But we must remain flexible, because the need to reverse course is not rare—not in hiking mountains and not in the practice of medicine. One team of researchers went through a year’s worth of *New England Journal of Medicine* (from 2009) and found that 16 (13%) of the 124 articles that made a claim about a medical practice directly contradicted what was standard medical practice.1 The team noted that the main reason a worthless or damaging practice had been adopted was, chillingly, “confidence that the pathophysiologic concepts underlying the practice were rational.”

That sounds a lot like the time I thought climbing Mount St. Helens mid-season seemed rational, too.

Regards,

Jon O. Neher, MD

Diving for PURLs

PURLs Criteria

Relevant: Is the topic relevant to family medicine? Yes
Valid: Are the findings scientifically valid? Yes
Change in practice: Would this change practice? Yes
Medical care setting: Is this implementable in clinic, etc? Yes
Implementable: Can we implement this immediately? Yes
Clinically meaningful: Are results clinically meaningful? No

Modifying the Phalen’s test: Increasing the sensitivity of a diagnostic maneuver for carpal tunnel syndrome


Neurologists developed and validated a new modified Phalen’s test for carpal tunnel syndrome. Two trained examiners tested 66 hands of 37 patients who presented to a neurology clinic, comparing the modified Phalen’s test and the traditional Phalen’s test with the gold standard of electrodiagnostic studies.

The traditional Phalen’s test is carried out by holding both hands in a fixed, flexed position for 60 seconds. The modified Phalen’s test adds applying a 2.83-unit monofilament test to the palmar lateral side of each finger’s distal phalanx 3 times. Testing is positive when the patient does not feel the monofilament in 1 or more fingers in the median nerve distribution (radial 3.5 fingers on the palmar side).

The traditional Phalen’s test yielded a specificity of 100% and sensitivity of 50% compared with electrodiagnostic studies. The modified Phalen’s test yielded a specificity of 100% with a sensitivity of 85%.

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Bottom line: The modified Phalen’s test is more sensitive than the traditional Phalen’s test for diagnosing carpal tunnel syndrome. Use the modified Phalen’s test when assessing patients with suspected carpal tunnel syndrome.

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

Vitamin D plus calcium supplementation reduces fracture risk only in institutionalized postmenopausal women


This meta-analysis for the US Preventive Services Task Force included 16 RCTs that examined the effect of vitamin D supplementation with and without calcium on fracture risk (at any site) in primarily postmenopausal white women.

The 5 RCTs (N=14,583) comparing vitamin D (400–1,370 IU/d) supplementation with placebo did not show a reduction in fracture risk (pooled RR 1.03; 95% CI, 0.84–1.26). The 11 RCTs (N=52,915) comparing combined vitamin D (300–1,000 IU/d) plus calcium (500–1,200 mg/d) supplementation with placebo showed a reduction in overall fracture risk (pooled RR 0.88; 95% CI, 0.78–0.99). However, results differed by study setting.

Institutionalized older adults (n=3,998) experienced a significant reduction in risk (RR 0.71; 95% CI, 0.57–0.89), while community-dwelling adults (n=43,549) did not (RR 0.89; 95% CI, 0.76–1.04). One RCT in postmenopausal women (N=36,282) found increased risk of renal and urinary tract stones (HR 1.17; 95% CI, 1.02–1.34) with combined supplementation with calcium plus vitamin D.

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Bottom line: While daily supplementation with 400–1,000 IU vitamin D plus 500–1,200 mg calcium may reduce the risk of fracture among institutionalized postmenopausal women, this meta-analysis was unable to find a benefit among community-dwelling postmenopausal women.

Review Author and Summary Author: Jennifer Bello, MD, The University of Chicago, Department of Family Medicine, Chicago, IL

We invite your questions and feedback. Email us at EBP@fpin.org.
**Prevent recurrent VTE with aspirin**


This multicenter, double-blind RCT compared the effect of aspirin versus placebo on the risk of recurrent venous thromboembolism (VTE) in patients who had just completed a several month course of warfarin. Study participants were age 18 or older with first-ever, objectively confirmed VTE. Patients were excluded if they had an underlying predisposition to VTE, intolerance to aspirin, or need to take anticoagulation for reasons other than VTE. The primary outcome was confirmed recurrent VTE, determined by computed tomography or compression ultrasonography. The primary safety outcome was major bleed, defined as fatal, occurring in critical locations, associated with a 2.0-g/dL drop in hemoglobin, or associated with a need for ≥2 units of transfusion.

A total of 403 patients were randomly assigned to receive aspirin 100 mg daily or placebo, and then were followed for 2 years with a possibility to extend if necessary. The median age of the study participants was 61 years, >60% were male, and 99% were Caucasian.

Of the 205 patients in the aspirin group, 28 developed recurrent VTE compared with 43 of the 197 patients in the placebo group during a median treatment period of 24.6 months (6.6% vs 43% per year; HR 0.58; 95% CI, 0.36–0.93). The number needed to treat to prevent 1 recurrence of VTE was 12.5. Two episodes of nonfatal major bleeding occurred: 1 in the placebo group due to a gastric ulcer and 1 in the aspirin group due to bowel angiodysplasia.

**Bottom line:** This study provides compelling evidence for the effect of 100 mg/d aspirin for the prevention of recurrent VTE. Although the 100-mg dose is not available in the United States, the available 81-mg dose provides comparable antiplatelet effects. The authors recommended that patients who experience VTE begin 81 mg/d aspirin to be continued indefinitely to prevent recurrence.

**Facilitated physical activity for depression**


This unblinded RCT compared the efficacy of facilitated physical activity for treatment of depression (facilitation included telephone motivational interviewing and behavioral guidance over 6–8 months) with usual care alone. Adult participants with a recent diagnosis of mild to moderate depression (N=361; mean Beck Depression Inventory score of 32 on a scale of 0 to 63) in a current depressive episode were identified in general practices.

Patients were stratified by baseline characteristics: antidepressant use, severity of depression, and baseline physical activity. The goal level of physical activity was 150 minutes of moderate to vigorous exercise per week. Usual care included antidepressant therapy, counseling, exercise prescriptions, or secondary mental health services.

Compared with the usual care group, more participants in the facilitation group met the goal for physical activity (52% vs 43% at the 4-month follow-up, 63% vs 49% at the 8-month follow-up, and 58% vs 40% at the 12-month follow-up; adjusted composite OR for all time points 2.27; 95% CI, 1.32–3.89). However, the physical activity facilitation group showed no mood change at the 4-, 8-, and 12-month follow-ups (difference in composite mean Beck Depression Inventory score at all time points –1.2; 95% CI, –3.4 to 1) based on intention-to-treat analysis. The facilitation group did not have lower antidepressant use or higher depression recovery rates (defined as Beck Depression Inventory scores <10).

**Bottom line:** Although this protocol did increase sustained participation in moderate exercise consistent with current recommendations, it did not improve depression. However, usual care may have varied considerably because physicians were unblinded. This negative study may discourage implementation of physical activity for treatment of depression; other regimens with more vigorous exercise goals warrant further investigation.

**Review Authors and Summary Authors:** Pooja Saigal, MD, NorthShore University Health System, and Umang Sharma, MD, University of Chicago, Department of Family Medicine, Chicago, IL
Does treatment of osteoporosis in bedbound patients reduce fractures?

Bottom line
In bedbound patients with osteoporosis, treatment with bisphosphonates improves bone mineral density and may reduce fractures.

Evidence summary
Osteoporotic fractures occur in bedbound patients, sometimes with as little force as turning the patient or changing a diaper. Therapy to prevent osteoporosis may not be prescribed for bedbound patients because of the misperception that these patients are not at risk of fracture because they are nonambulatory and at low risk of falls. Most osteoporosis studies have specifically excluded bedbound patients, so no study directly addressed this question.

Indirect evidence can be found in a bone loss study in paraplegic patients and a few studies on treatment of patients with stroke. In the paraplegia study, 13 patients with spinal cord injury (average age 30 years) and 15 controls were monitored for bone turnover with serum osteocalcin, parathyroid hormone, and calcitonin levels. Most bone loss occurred during the first 3 months after the injury causing paraplegia. A similar pattern of bone loss was found in 16 patients with immobility after stroke. More indirect evidence is found in a case-control study (N=1,139 patients with stroke, average age 77 years) in which hip fracture rates were 2 to 4 times higher in stroke patients than reference patients.

Two RCTs indicate that preventive treatment for osteoporosis appears to reduce the risk of fracture in patients after stroke, although the differences in fracture rates only reached statistical significance for men. Investigators for 1 RCT randomized 374 community-dwelling women older than 65 years after a stroke to 2.5 mg risedronate daily or placebo. There was 1 hip fracture in the bisphosphonate group in 1 year compared with 7 in the placebo group (calculated RR 0.14; 95% CI, 0.017–1.15). In the other trial, there were 2 hip fractures in the treated group over 18 months compared with 10 hip fractures in the placebo group (RR 0.19; 95% CI, 0.04–0.89). Extrapolation was difficult in both studies because patients had to be ambulatory to be enrolled and treatment was delayed for 3 months after stroke.

More directly relevant to the clinical question posed was a study of 27 patients aged 40 to 89 years (mean age 70.6 years) who were previously walking but unable to ambulate after a stroke. Patients were still hospitalized from the stroke when randomized to placebo or treatment with a single dose of 4 mg zoledronic acid within 35 days of stroke.

Patients in the placebo group (n=13) lost more hip bone mineral density than the treated group (~5.5% vs 0.0%, respectively). Although 72% of patients sustained a fall and the median number of falls was 2, no fractures occurred during the 1-year follow-up in either group.

The supporting evidence for treating bedbound patients to prevent fractures is limited; however, bone loss and fractures occur in bedbound patients and treatment of bedbound patients with a bisphosphonate after stroke, as expected, preserves bone density at the hip. The number of patients in the only study comparing nonambulatory stroke patients, however, was too small to show any difference in fracture risk or even document any fractures. Still, it appears reasonable to recommend treatment with bisphosphonates and to prescribe them early after patients become bedbound, as most bone loss occurs during the first 3 months.

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REFERENCES
How soon after diagnosing a patient with new-onset congestive heart failure should you start beta-blocker therapy?

A 60-year-old man with history of myocardial infarction 2 years ago, hyperlipidemia, hypertension, and a 30 pack-year history of smoking presents to the emergency department with complaint of progressive shortness of breath and lower extremity edema for 6 weeks. He is admitted to the hospital and subsequent workup reveals diagnosis of new-onset systolic heart failure. Beta-blocker therapy is indicated, but how soon should beta-blocker therapy be started in this patient?

**Bottom line**

A patient with newly diagnosed systolic heart failure (HF) should be started on a beta-blocker in the hospital, once volume status is optimized. At a minimum, this will result in a greater probability that beta-blocker therapy will be used over the next few months.

**Review of the evidence**

A 2004 prospective, randomized, open-label trial evaluated the predischarge initiation of beta-blocker therapy in 363 patients with HF (ejection fraction [EF] <40%) compared with postdischarge initiation.\(^1\) Patients were randomized to receive carvedilol 3.125 mg p.o. BID prior to discharge once deemed stable (and >12 doses prior to discharge) or to physician-discretion postdischarge carvedilol initiation. Patients were excluded if they had received a beta-blocker within 30 days or had NYHA class IV requiring inotropic support.

At the 60-day follow-up, patients in the predischarge arm were more likely to be on a beta-blocker than patients in the physician-discretion arm (91% vs 73%; \(P<.0001\)). There was no difference in discontinuation of beta-blocker due to intolerance or adverse effects (hypotension, bradycardia, worsening HF) between the 2 groups (10.6% vs 10.5%; \(P=\text{NS}\)). There was also no difference in the composite outcome (death, rehospitalization, unscheduled visit for HF, or increase in diuretic therapy) between the 2 groups (45% vs 46%; \(P=.9\)).\(^1\)

An observational trial of 2,373 patients hospitalized for HF (EF <40%) and eligible for beta-blocker therapy examined the beta-blocker dosing before, during, and after the first 60 to 90 days after hospital discharge.\(^2\) Out of this cohort, 632 patients (27%) were newly started on beta-blockers. Ninety-two percent of patients newly started on beta-blockers during hospitalization remained on therapy at the 60- to 90-day follow-up, compared with 94% of the entire cohort (no \(P\) given).

Another observational trial examined registry data of performance measures for 5,791 patients hospitalized for HF.\(^3\) At 60 to 90 days postdischarge, patients who received a beta-blocker prior to discharge had a significantly lower mortality risk (HR 0.42; 95% CI, 0.27–0.63) and a lower mortality or rehospitalization risk (HR 0.69; 95% CI, 0.52–0.91) compared with patients who did not receive a beta-blocker prior to discharge. This review did not separate out those patients with newly diagnosed HF or new beta-blocker therapy.

**Recommendations**

According to 2009 American College of Cardiology Foundation/American Heart Association evidence-based HF guidelines, beta-blocker therapy should be initiated when volume status has been optimized and optimally before discharge from the hospital (no grade provided).\(^4\)

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**REFERENCES**


How long should anticoagulation be continued in a patient after a DVT?

Evidence-Based Answer
Anticoagulation treatment of a primary deep vein thrombosis (DVT) should continue for at least 3 months (SOR: A, meta-analysis). In patients with a second unprovoked DVT and a low to moderate bleeding risk, extended therapy of longer than 3 months should be considered. Patients with cancer should receive extended therapy, preferably with low-molecular-weight heparin (LMWH), regardless of bleed risk (SOR: B, evidence-based guideline).

A 2011 meta-analysis of 7 RCTs that included 2,925 patients with their first venous thromboembolism who did not have cancer assessed risk of recurrence after stopping treatment.1 Patients were treated with warfarin (target INR of 2–3 or 2–2.85) for 1, 1.5, 3, 6, 12, or 27 months and followed for 24 months after stopping therapy.

Patients treated for 1 to 1.5 months had a higher risk of recurrent DVT than patients treated for 3 months or longer (HR 1.5; 95% CI, 1.2–2.0). There was no increased risk of recurrent DVT with 3 months of treatment compared with 6 months or longer (HR 1.2; 95% CI, 0.86–1.7). Comparing 3 months of treatment directly to 6 months of treatment, there was no difference in recurrent DVT risk (HR 0.8; 95% CI, 0.51–1.3).1

A 2000 meta-analysis of 7 RCTs (2,304 patients taking warfarin with a target INR of 2–3) compared recurrence rates of DVT and/or pulmonary embolism (PE) after 2 different durations of oral anticoagulant therapy for a first episode of DVT and/or PE.2 The recurrence rate was lower in patients receiving anticoagulation for 12–24 weeks (6.4%) compared with patients receiving anticoagulation for 3–6 weeks (11%) (RR 0.60; 95% CI, 0.45–0.79). No significant difference in the occurrence of major hemorrhage was found between groups.

Evidenced-based guidelines from the American College of Chest Physicians recommend more than 3 months of anticoagulation therapy for the first unprovoked proximal DVT in patients with a low to moderate bleed risk (Grade 1B, strong recommendation based on moderate evidence).3 In patients with a second unprovoked DVT, extended therapy (>3 months) should be considered in patients with a low (Grade 1B) or moderate (Grade 2B) bleed risk; those with a high bleed risk should be treated for 3 months (Grade 2B). In patients whose first proximal DVT is provoked by surgery, anticoagulation therapy is recommended for 3 months, regardless of bleed risk (Grade 1B). In patients with cancer, extended therapy should be given regardless of bleed risk (low to moderate bleed risk [Grade 1B]; high bleed risk [Grade 2B]); LMWH is recommended over vitamin K antagonist in patients with cancer. Extended therapy should be reassessed annually.

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How effective are lower extremity compression devices for reducing DVT risk after a stroke?

Evidence-Based Answer
Graduated compression stockings (GCS) and intermittent pneumatic compression devices (IPC) are equally effective for deep vein thrombosis (DVT) prophylaxis after acute stroke (SOR: A, meta-analysis). However, thigh-length GCS have a 5% risk of skin breakdown in patients without known peripheral vascular disease (SOR: B, RCT). Guidelines recommend using IPC or prophylactic-dose heparin for patients with acute stroke and restricted mobility (SOR: B, evidence-based guideline).

A Cochrane review of 4 RCTs assessed physical methods for preventing DVT after a stroke.1 Two RCTs compared IPC (177 patients) and 2 RCTs compared GCS (2,615 patients) with best medical treatment (described as early mobilization, hydration, and antiplatelet or anticoagulant drugs). Prophylaxis was started within 3 days of hospital admission in the studies.

Overall, during the treatment period, no significant difference was noted in DVTs with compression...
In patients with decompensated CHF, does BNP level correlate with clinical severity?

**Evidence-Based Answer**

B-type natriuretic peptide (BNP) levels appear to be **inversely correlated** with left ventricular ejection fraction (LVEF) and are higher in patients with decompensated congestive heart failure (SOR: C, small cohort studies). The clinical utility of this association is unclear.

A prospective study of 113 patients (78 men, mean age 67 years) with congestive heart failure (CHF) evaluated the clinical usefulness of myocardial scintigraphy and serial BNP. Overall, 30 patients had New York Heart Association (NYHA) class I disease, 61 patients had NYHA class II disease, and 22 patients had NYHA class III disease.

By echocardiography, mean LVEF was significantly higher in patients with ischemic heart disease than in patients with nonischemic disease (49% vs 44%; \( P < .03 \)). There was a significant negative correlation between BNP level and LVEF (\( r = –0.42; P < .00001 \)). However, there was no significant difference in BNP between patients with NYHA class III and those without (343 vs 267 pg/mL, respectively; \( P = \text{NS} \)). Also, there was no significant difference in BNP level in patients with HF due to nonischemic heart disease (45 patients with sarcoidosis, different cardiomyopathies, arrhythmias, or LV hypertrophy) compared with patients with HF due to ischemic heart disease (68 patients with acute coronary syndrome, acute or old myocardial infarction, ischemic cardiomyopathy, or unstable angina pectoris) (328 vs 255 pg/mL, respectively; \( P = \text{NS} \)).

A prospective study evaluated BNP levels in patients with decompensated CHF (DCHF; defined according to European Society of Cardiology guidelines and further classified by NYHA symptom criteria). Thirty-five male patients with known heart valve disease were enrolled: 20 patients had DCHF (mean age 68 years; 10% NYHA class I; 25% NYHA class II; 45% NYHA class III; 20% NYHA class IV) and 15 patients had nondecompensated CHF (mean age 71 years; 60% NYHA class I; 40% NYHA class II). The LVEF was significantly lower in the DCHF group compared with the control group (37% vs 61%; \( P < .001 \)). BNP levels were significantly elevated in the DCHF group compared with the control group (239 vs 255 pg/mL; \( P < .001 \)).

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A prospective study compared the relationship between BNP levels and LVEF measured by echocardiography in patients with CHF. Twenty-nine patients with NYHA class IV disease and 5 patients with NYHA class III disease were enrolled. When the subjects were grouped according to their BNP levels using a cutoff of 578 pg/mL (median BNP value), the mean LVEF was significantly lower in the group with BNP >578 pg/mL (49% vs 61%; \( P=.027 \)).

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In a patient with hyperlipidemia, what target triglyceride level should be used to eliminate the risk of pancreatitis?

Evidence-Based Answer
Triglyceride levels of more than 500 mg/dL are associated with a higher risk of acute pancreatitis and should be treated (SOR: C, conflicting guidelines and observational studies).

The guidelines from the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) suggest that a triglyceride level of more than 500 mg/dL should be treated to decrease the risk of acute pancreatitis. This guideline is based on expert opinion and a retrospective review of 52 patients with clinical evidence of pancreatitis whose triglyceride levels were measured at the peak of their pain. The distribution of triglycerides was bimodal, with 26 patients having levels between 10 and 800 mg/dL and 26 patients having levels >2,000 mg/dL. The authors noted that patients with lipemic-appearing (cloudy) serum were more likely to develop acute pancreatitis than patients with normal-appearing serum. Subsequent analysis of human serum suggested that blood became lipemic when triglyceride levels reached approximately 1,000 mg/dL.

More recently, a task force of the Endocrine Society recommended treatment of fasting triglyceride levels >1,000 mg/dL to reduce acute pancreatitis risk. These guidelines were based on data from a prospective study of 19 patients who presented with elevated triglyceride levels and abdominal pain clinically consistent with pancreatitis (confirmed when possible with laboratory data). Triglyceride levels ranged from 880 to 9,530 mg/dL (mean 4,336 mg/dL). The authors subsequently measured triglyceride levels in 65 adult hyperlipidemic family members of the index patients, and their mean triglyceride concentration was 284 mg/dL. None of the 65 pain-free relatives had triglyceride levels that exceeded 1,000 mg/dL.

In a case review of 1 patient who experienced 4 separate episodes of acute pancreatitis over 3 years, triglyceride levels during each episode measured more than 900 mg/dL (range 980–2,074 mg/dL). Each episode occurred shortly after she stopped her hypolipidemic agent, leading authors to conclude that hypertriglyceridemia may have led to pancreatitis.

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What is the most cost-effective method for treating venous stasis ulcers?

Evidence-Based Answer
Compression therapy is effective and reduces the overall costs of venous ulcers. Medical compression stockings appear to be more effective than bandages for this purpose. Pentoxifylline given with compression therapy further speeds healing (SOR: A, systematic review of RCTs). Aspirin may also speed healing (SOR: B, single RCT).

A Cochrane systematic review of 39 RCTs (N=3,796) evaluated the clinical effectiveness of compression bandages or stockings for the treatment of venous leg ulcers (VLU). Seven of the RCTs (N=689) compared compression therapy with no compression. Heterogeneity precluded pooling all 7 trials, but the
authors concluded that venous ulcers healed more rapidly and with lower overall cost with compression therapy than without. In the largest trial (N=233) the compression group healed in 20 weeks versus 43 weeks without compression ($P = .03$). Five trials included in the above Cochrane review specifically compared the effectiveness of a 4-layer bandage system (more commonly used in the United Kingdom) with the “Unna boot” (a less expensive system favored in the United States). Pooled data from 2 of these trials (N=71) revealed no significance difference between the 2 systems in complete healing at 1 year (RR 1.3; 95% CI, 0.78–2.3). Data from the 2 largest and most recent trials (N=201) could not be pooled but neither demonstrated any significant differences in complete healing between the 2 systems at 6 months and 1 year.

A meta-analysis of 8 RCTs (6 included in Cochrane review above) including 692 patients compared the effectiveness of calf-length medical compression stockings (MCS) with various compression bandages in healing VLU. MCS were more effective than other bandages in healing VLU (OR of failure 0.44; 95% CI 0.32–0.61). Time to healing (in weeks) was less with MCS (standard mean difference [SMD] –0.33; 95% CI, –0.50 to –0.16) and averaged 3 weeks shorter when compared with compression bandages.

A Cochrane review of 42 RCTs (N=3,001) evaluated the effectiveness of various wound dressings (hydrocolloids, foams, alginates, hydrogel dressings, and gauze) used under compression dressings or hosiery in the treatment of VLU. In 2011, a systematic review of 26 novel non–FDA-approved potential ocular antihypertensive compounds assessed their efficacy, safety, mode of IOP reduction, and pharmacology. One compound discussed was palmitoylethanolamide (PEA), an endogenous fatty acid that acts at cannabinoid-like receptors. In a prospective, randomized, double-blind, crossover clinical trial, 42 patients with open-angle glaucoma or ocular hypertension were given oral PEA (300-mg tablets twice a day) or placebo (PEA vehicle tablets twice a day) for 2 months (period 1) and, after a 1-month washout,

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What is the efficacy of cannabinoids in the treatment of glaucoma?

Evidence-based Answer
Low-dose cannabinoids temporarily decrease intraocular pressure (SOR: C, disease-oriented outcome). However, a consensus opinion guideline from the American Glaucoma Society recommends against its use (SOR: C, consensus opinion).

A prospective, randomized, placebo-controlled trial evaluated mucosal delivery of Δ-9-tetrahydrocannabinol (Δ-9-THC) and cannabidiol (CBD) in 6 patients with ocular hypertension or early primary open-angle glaucoma. Participants were given 5 mg Δ-9-THC, 20 mg CBD, 40 mg CBD, or placebo in this 1-time, single-dose study. The 5-mg sublingual dose of Δ-9-THC temporarily reduced intraocular pressure (IOP) versus placebo (24 vs 27 mmHg, $P = .026$), while 20 mg CBD showed no change. At 40 mg, CBD produced a transient increase in IOP versus placebo (23–26 mmHg; $P = .028$).

In 2011, a systematic review of 26 novel non–FDA-approved potential ocular antihypertensive compounds assessed their efficacy, safety, mode of IOP reduction, and pharmacology. One compound discussed was palmitoylethanolamide (PEA), an endogenous fatty acid that acts at cannabinoid-like receptors. In a prospective, randomized, double-blind, crossover clinical trial, 42 patients with open-angle glaucoma or ocular hypertension were given oral PEA (300-mg tablets twice a day) or placebo (PEA vehicle tablets twice a day) for 2 months (period 1) and, after a 1-month washout,
received the other treatment for 2 months (period 2). IOP was measured in all groups at the 1- and 2-month time marks.

For the PEA-treated groups in both study periods, at 1 and 2 months, respectively, the mean IOP reduction was 3.2 mmHg (14.7%) and 3.5 mmHg (15.9%; ANOVA \( P < .001 \)). This agent has been evaluated only in Italy and is not available in the United States.2

The American Glaucoma Society recommends against smoking marijuana for glaucoma, citing its short duration of action, psychoactive potential, and the harmful effects of marijuana smoke on the lungs.3

How effective is salt restriction in treating hypertension?

Evidence-Based Answer
In hypertensive patients, salt restriction decreases systolic blood pressure by 1 to 4 mmHg and diastolic pressure by 0.5 to 4 mmHg when the diet is maintained >6 months. Shorter periods of salt restriction yield slightly greater reductions (5 mmHg for systolic and and 2.5 mmHg for diastolic blood pressures) (SOR: C, systematic reviews of disease-oriented outcomes).

Cardiovascular disease (CVD) is associated with significant morbidity and mortality as well as substantial health care costs. In 2007, the World Health Organization released its guidelines for the primary prevention of CVD and recommended limiting daily salt intake to <5 g/d to reduce the incidence of hypertension.1

A 2011 Cochrane review of 7 RCTs with 6,489 participants focused on the cardiovascular benefits of reduced salt intake in adults over periods of longer than 6 months.2 The intervention groups received initial and follow-up education on salt reduction and diets targeting between 70 and 100 mmol/d or <80 mmol of daily sodium intake.

A meta-analysis of the hypertensive subgroups (2 trials; N=758 patients) followed for 24 or 30 months yielded a decrease in systolic blood pressure of 4.1 mmHg (95% CI, 5.8–2.4) and diastolic pressure of 3.7 mmHg (95% CI, 8.4–0.93) compared with control groups who received no dietary education. Neither all-cause mortality nor cardiovascular morbidity was altered in salt-restricted individuals. The authors noted that the analysis was underpowered to be conclusive regarding the positive or negative effects of salt restriction.2

A 2008 Cochrane meta-analysis of 20 RCTs with 802 individuals focused on the effects of reduced salt intake on blood pressure over periods as short as 4 weeks.3 The intervention groups had a daily salt intake of 3.4 to 7.4 g, which correlated with a net reduction of 3.1 to 6.9 g/d of dietary salt intake (vs the usual salt intake of 9.5 g/d).

Of the 19 RCTs (number of patients not defined) in this review that followed systolic blood pressures in hypertensive patients compared with a control group, a 5.1-mmHg reduction was noted (95% CI, 4.3–5.8). In the 21 studies (number of patients not defined) in this review that followed diastolic blood pressures in hypertensive patients compared with a control group, a 2.7-mmHg reduction was noted (95% CI, 2.2–3.2). The trials ranged from 4 weeks to 1 year (median 5 weeks).3

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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 Navy or the US Navy Service at large.


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Are lorcaserin and phentermine plus extended-release topiramate safe and effective for weight loss?

Bottom line

The FDA recently approved the use of a new selective serotonin 2C (5-HT2C) receptor agonist, lorcaserin (Belviq®), and a new fixed-dose combination of the sympathomimetic amine phentermine and an extended-release form of the antiepileptic drug topiramate (Qsymia®), as adjuncts to a reduced-calorie diet and increased physical activity for chronic weight management in obese adults. Both are indicated in patients who have a body mass index (BMI) ≥30 kg/m² or who are overweight (BMI ≥27 kg/m²) with at least 1 weight-related comorbidity.

Evidence summary

Lorcaserin

The safety and efficacy of lorcaserin was evaluated in a RCT of adult patients with a BMI >30 kg/m² or >27 kg/m² with 1 weight-related condition (hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, or sleep apnea). The trial did not include subjects with diabetes or with existing moderate to severe valvulopathy.

A second RCT evaluated the safety and efficacy of lorcaserin in adults with a BMI >30 kg/m² or a BMI of 27 to 29.9 kg/m² with hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea. Subjects who had cardiovascular events, surgery, diabetes, blood pressure >150/95 mmHg, or hypertriglyceridemia were excluded.

A smaller RCT included patients with comorbidities such as hypertension and diabetes. Patients taking insulin, exenatide, pramlintide, or patients with a change in cigarette use, cancer, surgery, epilepsy, depression, or other mental health conditions were excluded.

In all 3 trials, lorcaserin 10 mg was given once or twice daily and lifestyle modification measures were utilized for all patients. Outcomes after 1 year of therapy are shown in TABLE 1.

Because weight loss drugs affecting 5-HT2C have previously caused valvulopathy, this adverse effect was evaluated. At year 1 in one trial, valvulopathy developed in 2.3% of patients receiving placebo and 2.7% of patients receiving lorcaserin (RR 1.1; 95% CI, 0.69–1.85). At the 2-year follow-up, the rate of valvulopathy was 2.7% in patients receiving placebo and 2.6% in patients receiving lorcaserin. In another trial, the incidence of valvulopathy was 2.0% for subjects receiving lorcaserin BID and placebo (95% CI, 1.2–2.8 for both). Other adverse effects reported in all 3 trials, such as headache, nausea, dizziness, and fatigue, were relatively benign.

Phentermine/topiramate

FDA approval of Qsymia was based largely on the results of 3 large RCTs (TABLE 2), which were all about 1 year in length. One RCT (known as the CONQUER study) evaluated weight loss in adults with a BMI >27 kg/m² and ≥2 comorbid conditions (hypertension, lipid disorders, glucose intolerance, or diabetes mellitus) receiving phentermine/topiramate at 2 different doses or placebo. The trial excluded patients with BP >160/100 mmHg, fasting blood glucose >240 mg/dL, triglycerides >400 mg/dL, type 1 diabetes, and those receiving diabetes medications other than metformin. At the higher dose, adverse effects with phentermine/topiramate included dry mouth (21% vs 2% for placebo), paresthesia (21% vs 2%), constipation (17% vs 6%), insomnia (10% vs 5%), dizziness (10% vs 3%), and taste disorder (10% vs 1%).

Another RCT included adult patients with a BMI ≥35 kg/m², triglycerides ≤200 mg/dL with ≤1 drug, blood pressure ≤140/90 mmHg with ≤2 drugs, and

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Intervention</th>
<th>Mean percentage decrease in weight vs placebo at 1 year (P value)</th>
<th>Proportion losing ≥5% of body weight vs placebo at 1 year (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,182²</td>
<td>10 mg BID vs placebo</td>
<td>5.8% vs 2.2% (.001)</td>
<td>48% vs 20% (.001)</td>
</tr>
<tr>
<td>4,008¹</td>
<td>10 mg BID vs placebo</td>
<td>5.8% vs 2.8% (.001)</td>
<td>47% vs 25% (.0001)</td>
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<td>10 mg QD vs placebo</td>
<td>4.7% vs 2.8% (.001)</td>
<td>40% vs 25% (.0001)</td>
</tr>
<tr>
<td>604⁴</td>
<td>10 mg BID vs placebo</td>
<td>4.5% vs 1.5% (.001)</td>
<td>38% vs 16% (.001)</td>
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<tr>
<td></td>
<td>10 mg QD vs placebo</td>
<td>5.0% vs 1.5% (.001)</td>
<td>45% vs 16% (.001)</td>
</tr>
</tbody>
</table>
fasting serum glucose ≤110 mg/dL. The exclusion criteria were not disclosed in this study. Adverse effects with phentermine/topiramate included paresthesia (19% vs 1.9% for placebo), dry mouth (17% vs 3.7%), constipation (14% vs 6.8%), and taste disorder (8.4% vs 1.0%).

The final RCT included patients who had completed the CONQUER trial, thus the same exclusion and inclusion criteria were used. The aim of this trial was to demonstrate long-term (additional 1 year) safety and efficacy. The same adverse effects with phentermine/topiramate were observed, but at diminished rates: paresthesia (3.4% vs 0% for placebo), constipation (4.1% vs 3.1%), and dry mouth (1.4% vs 0.4%).

Preliminary safety data raised concerns that phentermine/topiramate may be teratogenic. Due to this finding, approval of Qsymia required a risk evaluation and mitigation strategy (REMS). The REMS permits only specially certified pharmacies to dispense Qsymia.

Conclusion
Belviq and Qsymia along with appropriate lifestyle modifications are both effective treatments for obesity as long as benefits versus risks of adverse effects are taken into account. Patients taking Belviq had an approximately 5% reduction in body weight, while patients taking Qsymia had an 8% to 10% reduction depending on the dose. Although Qsymia appears to be more effective than Belviq, it has a more extensive side effect profile.

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REFERENCES
1. An older adult has an acute stroke and is bedbound for 3 months. As the patient's clinician, you can be sure that
   a. Significant bone loss will occur during the first 3 months
   b. Zoledronic acid will not alter bone loss while the patient is bedbound
   c. Zoledronic acid will reduce the risk of falls
   d. The risk of hip fracture is reduced

2. In a hospitalized patient with new-onset heart failure that has been fluid optimized, early initiation of beta-blockers has been found to have which of the following outcomes?
   a. Increase in adverse effects
   b. Increase in chance of beta-blocker use at 60 to 90 days
   c. Half of patients will discontinue the beta-blocker by 60 to 90 days
   d. Increase in all-cause mortality

3. A 50-year-old woman with history of a prior unprovoked deep vein thrombosis (DVT) treated with 3 months of warfarin 2 years ago presents to the hospital with lower leg pain and swelling and is found to have a lower extremity DVT. The patient has no risk factors for bleeding at this time. How long should anticoagulation therapy be continued in this patient?
   a. 1 month
   b. 1.5 months
   c. 3 months
   d. Longer than 3 months

4. In patients with stroke, the use of thigh-length graduated compression stockings for deep vein thrombosis (DVT) prophylaxis has been found to:
   a. Increase the risk of skin breakdown
   b. Decrease the risk of proximal DVT compared with medical prophylaxis
   c. Decrease the risk of a DVT in the 30 days after a stroke compared with medical therapy
   d. Increase the risk of pulmonary embolism in the 30 days after a stroke compared with medical therapy

5. According to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), at what threshold should triglycerides be treated to prevent acute pancreatitis?
   a. >260 mg/dL
   b. >500 mg/dL
   c. >150 mg/dL
   d. >2,000 mg/dL

6. Elevated B-type natriuretic peptide values suggest:
   a. Good left ventricular function
   b. Poor left ventricular function
   c. Decompensated congestive heart failure
   d. B and C

7. Which of the following adverse events is more common with lorcaserin (Belviq®) than phentermine/topiramate (Qsymia®)?
   a. Paresthesia
   b. Headache
   c. Dry mouth
   d. Constipation

8. Which of the following statements is true about the efficacy of cannabinoids for glaucoma?
   a. The American Glaucoma Society recommends against the use of cannabinoids for the treatment of glaucoma
   b. Sublingual cannabinoids have been well studied and their administration has shown consistent lowering of intraocular pressure (IOP) in glaucoma patients
   c. While the cannabinoid receptor agonist SAD-448 applied via a single drop has not been shown to be effective in lowering IOP, application of multiple drops has shown efficacious reduction
   d. Palmitoylethanolamide (PEA) can lower IOP 0.05 to 1.0 mmHg more than latanoprost
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