EVIDENCE-BASED PRACTICE

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SPOTLIGHT ON PHARMACY
15 Antiarrhythmic agents to prevent sudden death in heart failure
Knock-off goods

I was in northern Thailand a few years ago, walking through one of that country’s boisterous street markets, admiring all the exotic goods on display. I was particularly intrigued by traditional Thai fabrics—shimmering textiles with threads of real gold and silver in the weave. Among the great stacks of traditional fabrics, however, I saw a lot of American designer clothes, particularly Nike hats, Nike shirts, and Nike light jackets. I wondered why Nike was trying to sell so much stuff in Thailand.

Later that evening, when some of the local workshops had their rusty steel roll doors up, I found out where all the Nike gear was coming from. Several entire workshops, filled with chain-smoking old men working foot-powered sewing machines, were embroidering Nike “swoops” on piles of cheap hats and T-shirts. (Tongue twister alert!) I suppose they saw that swoops sold, so they sewed swoops. Maintaining Nike quality was obviously not the goal.

Unfortunately for evidence-based medicine, similar economic forces have flooded the medical marketplace, not with fake swoops, but with low-quality meta-analyses. Dr. JP Ioannidis recently examined trends in number and quality of meta-analyses published in PubMed since 1986.¹ He noted meta-analysis production rose much faster than RCT production; we now have more meta-analyses produced than big research trials. Within 7 years, there were a crazy 185 meta-analyses of antidepressants, 80% written with some industry link. Not surprisingly, 70% completely avoided mentioning the negative effects of antidepressants. Certain companies now write meta-analyses for a fee (Mapi Group, Abacus International, Evidera, and Precision for Value, for example), fees paid for out of industry marketing budgets. Editorializing a bit, Dr. Ioannidis bemoaned that about 3% of meta-analyses were decently constructed and clinically useful. The other 97% were redundant, flawed beyond repair, not useful, evaluated discredited ideas, or were abandoned without publication.

So a meta-analysis is now something like a swoop in a Chiang Mai street market. It might signal high-quality work, or it may just cover up some low-quality junk. I will be turning both the shirts and the manuscripts inside out to check their quality before I buy.

REFERENCE
1. Ioannidis JP. The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. Milbank Q. 2016; 94(3):485–514.
Are IV or oral steroids better for treatment of acute COPD exacerbation?

**EVIDENCE-BASED ANSWER**

Intravenous (IV) steroids are no more effective than oral steroids for the initial treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD) and do not reduce risk of treatment failure, relapse, or mortality; moreover, IV steroids are associated with increased hyperglycemia (SOR: A, systematic review of RCTs). Initial treatment with oral steroids may be associated with lower costs and shorter hospital stay (SOR: B, retrospective cohort study).

**Evidence summary**

A 2014 Cochrane systematic review of 3 RCTs (N=298) compared oral and IV corticosteroids for the initial treatment of acute COPD exacerbation.¹ The studies included participants with mean ages 69 to 72 years and mean smoking history of 27 to 69 pack-years; the studies excluded patients having severe exacerbations, primarily defined by complications such as pneumonia or need for mechanical ventilation. The initial oral dose of corticosteroids was 32 mg methylprednisolone in 2 studies and 60 mg prednisolone in the remaining study; the initial IV dose was methylprednisolone 40 mg in 1 study, methylprednisolone 1 mg/kg per day in the second study, and 60 mg prednisolone in the third.

The 3 primary outcomes were treatment failure, defined as need for mechanical ventilation or change in therapy; relapse; and postdischarge mortality between 1 and 3 months. Secondary outcomes included length of hospital stay and risk of hyperglycemia.¹

In pooled results of all 3 trials, initial IV corticosteroids did not reduce treatment failure (odds ratio [OR] 0.67; 95% CI, 0.34–1.3), the risk of relapse (OR 0.95; 95% CI, 0.50–1.8), or the risk of mortality (OR 1.4; 95% CI, 0.44–4.5). Initial IV corticosteroids increased the incidence of hyperglycemia (1 trial, n=40; OR 4.9; 95% CI, 1.2–19.9). The review was limited by wide variation in cotreatment with nebulizers and subsequent corticosteroid tapers in the different studies.¹

A 2010 retrospective cohort study evaluated the effect of dose and route of corticosteroid administration in patients older than 40 years with acute COPD exacerbation, with a primary outcome of treatment failure—defined as mechanical ventilation, inpatient mortality, or readmission within 30 days.² The study included 79,985 patients (92% in IV cohort and 8% in oral cohort) who were admitted to 414 hospitals between January 2006 and December 2007. To be included, patients had to receive an oral dose between 20 and 80 mg prednisone equivalents or an IV dose between 120 and 800 mg prednisone equivalents on days 1 or 2. Patients were analyzed by intention-to-treat in the first 2 days. Treatment failure occurred in 10.9% of the IV group and 10.3% of the oral group (P=.13). To mitigate influence of disease severity on therapy selection, patients were propensity matched based on covariates.

In the propensity-matched nested cohort (n=12,402), patients who received oral therapy compared with IV were at lower risk of treatment failure (OR 0.84; 95% CI, 0.75–0.95), had a shorter length of hospital stay (3 vs 4 days; P<.001), and lower cost ($4610 vs $5189; P<.001).²

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**REFERENCES**


**Cold turkey or gradual approach for smoking cessation?**


This RCT compared abrupt (n=355) versus gradual (n=342) smoking cessation (75% reduction over 2 weeks prior to complete cessation) in adults recruited from British general practices who smoked at least 15 cigarettes per day, used 12.5 g of loose leaf tobacco daily, or had an end expiratory carbon monoxide concentration of at least 15 ppm and were willing to quit smoking 2 weeks after enrollment.

The primary outcome was Russell Standard abstinence (validated by exhaled CO concentration and salivary cotinine) at 4 weeks, 8 weeks, and 6 months. Participants in both groups were offered and encouraged to use nicotine replacement therapy and received weekly withdrawal-oriented behavioral therapy.

The 4-week abstinence rate for gradual cessation was lower than that for abrupt cessation (39% vs 49%; unadjusted relative risk [RR] 0.80; 90% CI, 0.66–0.93). Abstinence rates were higher for abrupt cessation at 8 weeks (RR 0.8; CI, 0.63–0.95) and 6 months (RR 0.71; CI, 0.46–0.91) as well.

Adverse effects included more salivating and cold sweats in the gradual cessation group in the 2 weeks prior to cessation. No difference was noted in withdrawal symptoms between the 2 groups. More subjects preferred the gradual reduction approach (50.9% vs 32.1%), but among those who had that preference, abstinence rates were lower independent of the group to which they were randomized.

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**Bottom line:** Smokers who stop smoking “cold turkey” have higher abstinence rates at 4 weeks, 8 weeks, and 6 months than those who gradually reduced smoking prior to a quit date. However, because more patients choose gradual smoking reduction, giving patients the choice through shared decision-making may lead to more abstinence overall.

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**BMI: A weak predictor of mortality in frail older women**


This prospective, cohort multicenter study evaluated the health risk associated with body mass index (BMI) in 11,070 frail older women in a subset of the Women’s Health Initiative Observational Study. Women were 65 to 84 years old and followed for an average of 11.5 years.

Presence of 3 of 5 parameters defined frailty: muscle weakness, slow walking speed, exhaustion, low physical activity, and unintentional weight loss. BMI was classified as follows: less than 18.5 (underweight); 18.5–24.9 (normal); 25.0–29.9 (overweight); 30.0–34.9 (class I obesity); 35.0–39.9 (class II obesity); and more than 40 (class III obesity). The association of BMI with mortality was examined, adjusted for race, education, income, smoking status, physical activity, cancer, cardiovascular disease, diabetes mellitus, and emphysema.

Mortality was greater for underweight patients with at least 1 comorbidity (hazard ratio [HR] 2.4; 95% CI, 1.8–3.0), but no association was found when no comorbidity was present (HR 1.2; 95% CI, 0.68–2.0). Mortality was lower for overweight cases (HR 0.80; 95% CI, 0.73–0.88) and class I obesity (HR 0.79; 95% CI, 0.71–0.88), with or without morbidity. Mortality was not different from normal weight cases for class II obesity (HR 0.93; 95% CI, 0.81–1.2) and class III obesity (HR 1.0; 95% CI, 0.85–1.2).

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**Bottom line:** In frail older women, these findings suggest modestly increased mortality rates associated with BMI for underweight, decreased mortality rates for overweight and mildly obese, and no difference among the moderately or severely obese. These small differences in prognosis do not justify any change in clinical approach.

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Is osteopathic manipulative treatment effective for low back pain management in pregnancy?

**Bottom line**
Osteopathic manipulative treatment (OMT) is safe and may reduce pain scores and improve back-related functioning during the third trimester of pregnancy compared with usual obstetric (OB) care (SOR: B, RCTs). However, it does not appear more effective than sham ultrasound (SOR: B, RCTs).

**CASE**
A 25-year-old presents for a routine prenatal visit at 30 weeks with left low back and hip pain for the last 2 weeks. She denies injury and has no history of back or hip pain. The patient does not want medications before the birth. She asks what else might help relieve her pain. On examination, she has left lumbar paraspinal muscle hypertonicity and anterior rotation of the sacral base on the left side.

**Evidence summary**
A 2015 RCT of 400 pregnant women evaluated OMT as a tool to reduce low back pain and improve back-related functioning during the third trimester of pregnancy.¹ Inclusion criteria included maternal age between 18 and 35 years, attained 30th week of gestation, absence of other body-based therapies, and absence of high-risk pregnancy. Patients were randomized to 3 groups: usual care only (UCO), usual care plus OMT (OMT), and usual care plus placebo ultrasound treatment (PUT). All obstetric providers were blinded to the subject’s group assignment.

The OMT group received 20-minute treatments 7 times. Techniques included soft tissue, myofascial release, decompression, articulation, and compression of the fourth ventricle of the brain (CV4).¹

Primary outcomes were measured using 2 questionnaires. Low back pain was measured with Quadruple Visual Analog Scale (QVAS) to score the pain intensity from 0 (pain-free) to 100. Back-related functioning was evaluated with Roland-Morris Low Back Pain and Disability Questionnaire (RMDQ), with higher scores indicative of greater functional disability.¹

Pain scores improved in the OMT and PUT groups (mean difference on QVAS –3.3 and –3.5, respectively); however, they worsened in the UCO group (mean difference 3.8). The OMT group had significantly improved pain scores compared with the UCO group, with a mean difference of –7.1 (95% CI, −3.1 to 3.4). Back-related functioning improved significantly with OMT versus UCO (RMDQ mean difference –2.3; 95% CI, –3.2 to –1.3), but not versus PUT (MD 0.21; 95% CI, −0.73 to 1.14).¹

A 2010 RCT of 144 women used a similar study design measuring the same primary outcomes as the 2015 study above.² The women were randomized to usual OB care (UOBC), UOBC and OMT (UOBC+OMT), and UOBC and sham ultrasound treatment (UOBC+SUT).

Similarly, the women had 7 treatment visits addressing the same anatomical sites; however, this study excluded the CV4 technique and treatment sessions were 30 minutes instead of 20 minutes. Demographic characteristics of the women were similar, although there was a statistical difference among the groups with illicit drug use. Fewer women were in the “never used” category for illicit drug use in the UOBC+OMT group (n=22) versus the UOBC+SUT group (n=38) or the UOBC only group (n=39). There were more women in the “former user” category in the UOBC+OMT group (n=11) versus the UOBC+SUT group (n=1) or the UOBC only group (n=2).²

The same primary outcomes were measured with the same questionnaires and rating tools. The back pain score for UOBC+OMT versus UOBC was 0.27 (95% CI, –0.13 to 0.68) and UOBC+OMT versus UOBC+SUT was 0.14 (95% CI, –0.26 to 0.55). Back-related functioning worsened significantly in all groups as pregnancy progressed, but significantly less so for UOBC+OMT than UOBC on the RMDQ, 0.72 (95% CI, 0.31–1.14). The difference in functional outcome with UOBC+OMT versus UOBC+SUT on the RMDQ was 0.35 (95% CI, –0.06 to 0.76).²

**CASE WRAP-UP**
You treat the patient with osteopathic techniques focusing on her lumbar paraspinal muscles and sacrum. She returns for treatments every 2 weeks with her OB visits. After 4 sessions, her symptoms were significantly improved.

**REFERENCES**
Does treatment with vitamin D supplementation improve patient outcomes in systemic lupus erythematosus?

**EVIDENCE-BASED ANSWER**

In patients with systemic lupus erythematosus (SLE) and vitamin D levels less than 30 ng/mL, oral supplementation with vitamin D 2,000 IU decreases disease activity (SOR: B, RCT). However, in a population of mixed vitamin D–sufficient and –insufficient patients, even high doses of vitamin D do not seem to affect disease activity (SOR: B, small RCT).

A 2013 RCT of 267 Egyptian patients with SLE and vitamin D levels less than 30 ng/mL (average age 39 years, 85% women; 88% follow-up) assessed whether vitamin D supplementation (2,000 IU/d) over 12 months would decrease disease activity compared with placebo as measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

Scores in the SLEDAI range from 0 to 105, with scores of 3.8 or more considered active disease.² The vitamin D group (n=178) and placebo group (n=89) were divided into those with baseline vitamin D deficiency (<10 ng/mL) and insufficiency (10–30 ng/mL). Within-group analysis showed the SLEDAI decreased in the vitamin D group from a mean of 4.9 before treatment to 3.2 after treatment in patients with vitamin D insufficiency (P=.01) and from 4.9 to 3 for vitamin D–deficient patients (P=.05). No significant change occurred in the placebo group (4.8–4.5 for insufficient patients and 4.9–4.6 for deficient patients). No direct comparison between the vitamin D group and placebo group was described. Limitations included low baseline disease activity and relatively low vitamin D dosing.

A 2015 crossover study of 34 northern Italian women with SLE and SLEDAI scores less than 6 (average age 32.5 years, 85% Caucasian) compared the effect of 2 vitamin D dosing protocols on disease activity.³ Patients were randomized to receive a standard regimen (SR) of 25,000 IU cholecalciferol monthly or an intensive regimen (IR) of a 300,000 IU bolus then 50,000 IU monthly for the first year. For the second year, treatment regimens were flipped. The combined mean baseline vitamin D level was 32 ng/mL, but 36% of patients in the SR and 60% in the IR group were vitamin D insufficient.

Only 3 patients (2 in the IR group and 1 in the SR group) experienced a disease flare, with SLEDAI scores increasing to 6 to 8. Excluding these patients, no significant change in SLEDAI was noted in either group, but actual results were not reported. Limitations included selection bias for patients with inactive disease.³

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Are cannabinoids taken orally an effective treatment for adults with chronic neuropathic pain?

**EVIDENCE-BASED ANSWER**

The answer is unclear. Nabilone and nabiximols, as adjuncts to any stable analgesia regimen including opioids, tricyclics, and anti-inflammatory medications, reduce neuropathic pain by 1 to 2 points more than placebo on 11-point pain scales. However, nabilone is not as effective as dihydrocodeine when the 2 are compared directly (SOR: B, small RCTs).

In 2012, a flexible-dose, double-blinded RCT compared the efficacy of nabilone as an adjunct to the treatment of diabetic peripheral neuropathic pain versus placebo.¹ The 4-week single-blinded run-in phase, 37 patients on a stable pain medication regimen including NSAIDs, gabapentin, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, opioids, or acetaminophen with pain rated more than 4 on a 0 to 10 numerical pain scale, received nabilone 0.5 to 2 mg BID.

Twenty-six patients achieved at least 30% pain relief and were advanced to the second double-blinded phase, during which they were randomly assigned to nabilone or placebo. The nabilone group continued their stable dose of nabilone.
for 5 weeks. Using a pain diary, the mean of the last 7 pain scale entries during the fifth week of the double-blind phase was compared with the mean score during the baseline week prior to the single-blind phase.¹

The mean pain score decreased by 3.0 in the nabilone group versus 1.1 in placebo group (P<0.01).¹

In 2007, a double-blind, placebo-controlled RCT examined the analgesic effect of nabiximols, using a European oromucosal preparation (Sativex), in patients with chronic unilateral neuropathic pain and allodynia for at least 6 months.² All 125 patients were older than 18 years and continued on their existing analgesic regimen. Participants were primarily Caucasian with pain refractory to their current analgesic regimen, with 68% on chronic opioids previously. After initial dosing, patients were able to self-titrate to a maximum dose of 8 sprays every 3 hours.

On average, patients were using 11 sprays of nabiximols daily, versus 19 daily in the placebo group. Each spray delivered 2.7 mg tetra-hydro-cannabinol and 2.5 mg cannabidiol. Analgesic effect was measured primarily on a 0 to 10 point numerical pain scale, which showed greater pain reduction with nabiximols by an average of 0.96 points (95% CI, 0.32–1.59) compared with placebo, when used adjunctively.²

There was no testing for drugs of abuse prior to the study starting. Twenty patients violated study protocol by failing to follow up in the given time frame, using prohibited medication, or violating inclusion or exclusion criteria.²

In 2008, a randomized, double-blinded crossover study compared the analgesic effect of nabilone versus dihydrocodeine in patients with chronic neuropathic pain.³ Participants were 24 to 84 years old with neuropathic pain, primarily postoperative or after injury, and poor pain control on their current analgesic regimen. Overall, 96 patients, all rating their pain more than 40 mm on a 0- to 100-mm visual analog scale (VAS), were randomized into 2 groups. The first group started nabilone as needed, with doses escalating from 0.25 to 2 mg over 6 weeks, followed by a 2-week washout phase, and then subsequently started on dihydrocodeine as needed, escalating from 30 to 240 mg over 6 weeks. The second group started first with dihydrocodeine.

Based on daily VAS recordings and weekly analysis of their means, nabilone had a higher mean VAS score than dihydrocodeine by 6 mm (95% CI, 1.4–10.5), indicating that dihydrocodeine provided better analgesia than nabilone. Thirty-three patients failed to complete the trial, and 9 did not comply with the trial drugs.³

**Evidence-Based Answer**

Simple office cystometrics are modestly useful in diagnosing or ruling out detrusor overactivity (DO) in women and very useful in men. They are also moderately useful for diagnosing or ruling out stress urinary incontinence (SUI) in women (SOR: B, meta-analysis of cohort studies). Multichannel urodynamic studies are preferred to simple or single-channel urodynamic studies as a part of a preoperative evaluation, although outcome data about the utility of urodynamic studies are lacking (SOR: C, consensus guideline).

A 2006 systematic review of 121 cohort studies evaluated the diagnostic accuracy of different strategies to diagnose urinary incontinence, including urodynamic studies.¹ Three cohort studies (n=403) evaluated standing single-channel cystometry (SCC), consisting of measuring the bladder volume at which an urge to void and involuntary bladder contractions occur compared with the gold standard of multichannel urodynamics (MCU), which was not described.

Pooled analysis revealed SCC was modestly effective for establishing the diagnosis of DO in women (sensitivity 63%, specificity 88%, positive likelihood ratio [LR+] 5.3, negative likelihood ratio [LR−] 0.42). Two cohort studies including a total of 238 elderly men and women found that supine SCC,
compared with MCU, was modestly effective at diagnosing DO in women aged 60 and older (n=180; sensitivity 74%, specificity 77%, LR+ 3.2, LR– 0.34), and was very effective at diagnosing DO in elderly men (n=58; sensitivity 89%, specificity 92%, LR+ 11, LR– 0.12). A single cohort study of 97 elderly women demonstrated that supine SCC compared with MCU had some utility for the diagnosis of SUI in women (sensitivity 86%, specificity 86%, LR+ 6.1, LR– 0.16).¹

A 2012 guideline on the use of urodynamic testing in the evaluation of lower urinary tract symptoms by the American Urological Association and Society for Urodynamics, Fetal Pelvic Medicine and Reconstruction recommended the use of MCU over SCC when patients are potential candidates for invasive, potentially morbid, or irreversible treatments for SUI or DO.² While information obtained by MCU may be used to formulate a specific treatment plan, data about the use of MCU and improved outcomes are lacking.

In adults with hypertension, does routine use of salt substitutes reduce blood pressure compared with routine use of sodium?

**EVIDENCE-BASED ANSWER**

Yes. In adults with hypertension, routine use of salt substitutes compared with standard sodium chloride (NaCl) lowers systolic blood pressure (SBP) by 6 to 13 mmHg and diastolic blood pressure (DBP) by 2 to 8 mmHg (SOR: C, based on a meta-analysis of RCTs and 2 other RCTs with disease-oriented outcomes).

A 2014 meta-analysis of 5 RCTs (N=1,974) studied the effects of salt substitutes on blood pressure in patients with hypertension.¹ Four studies were conducted in China and 1 in the Netherlands. Patients with hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg) were randomized to receive salt substitutes or common salt (99.8%–100% NaCl). Four trials used a substitute containing NaCl, potassium chloride (KCl), and magnesium salt. The other trial used a substitute containing NaCl, KCl, calcium salts, and folic acid. Trial duration ranged from 6 months to 2 years and all were limited by small sample sizes of fewer than 350 patients per group.

Salt substitute compared with common salt decreased SBP by 5.7 mmHg SBP (95% CI, 3.2–8.2) and decreased DBP by 2.4 mmHg (95% CI, 0.2–4.5).¹

A 2014 patient-blinded RCT evaluated the effects of a salt substitute on lowering blood pressure in 282 rural Tibetan adults aged 40 years and older with known hypertension (SBP ≥140 mmHg).² Patients in the intervention group received a salt substitute of 65% NaCl, 25% KCl, and 10% magnesium sulfate, and received 100% NaCl. The salt substitute reduced SBP by 7.6 mmHg and DBP by 3.5 mmHg more than standard salt (P<.05 for both SBP and DBP). More patients discontinued the salt substitute than the NaCl (27/141 vs 8/141, P value not given).

A 2015 Brazilian single-blinded RCT examined the effect of salt substitution on the blood pressure of 35 adults (SBP ≥140 mmHg, DBP ≥90 mmHg) 20 to 65 years old with uncontrolled hypertension taking stable doses of antihypertensive medications.³ Nineteen patients were randomized to receive a mixture of reduced NaCl plus KCl (approximately 67% less sodium than standard table salt) and 16 patients to the regular NaCl control group.

Compared with standard salt, salt substitute resulted in a mean decrease in SBP/DBP of 12.5/7.6 mmHg (P<.05 for both SBP and DBP). A major limitation of the study was the small sample size.³

Among patients with laboratory-confirmed influenza, does treatment with oseltamivir reduce morbidity and mortality?

**EVIDENCE-BASED ANSWER**
Yes, in the hospital. Treatment with neuraminidase inhibitors (NAI), most commonly oseltamivir, is associated with improved survival in hospitalized patients. Survival is higher when NAI treatment is started within 5 days of illness (SOR: B, retrospective cohort). For outpatient adults, oseltamivir reduces the duration of symptoms with uncomplicated influenza by about 1 day, even when treatment is started 48 hours or more after illness onset. Oseltamivir reduces the risk of lower respiratory tract complications and admittance to hospital (SOR: A, meta-analysis of RCTs).

A 2014 multicenter, retrospective cohort study (N=2,649) of hospitalized, higher morbidity patients evaluated all-cause 30-day mortality.¹ Patients were aged 17 or older, with laboratory-confirmed influenza. A large proportion of patients were infected by pandemic influenza. Of the enrolled patients, 1,991 (75.2%) were treated with NAI, of whom 1,956 (73.8%) were treated with either oseltamivir or an oseltamivir-containing regimen. NAI treatment was started within 2 days, 3 to 5 days, or after 5 days from illness onset in 45%, 21%, and 9.3% of patients, respectively.

Compared with no treatment, NAI treatment showed improved survival (adjusted hazard ratio [HR] 0.28; 95% CI, 0.19–0.43). Chance of survival was highest when NAI treatment was started within 2 days of illness compared with no treatment (adjusted HR 0.20; 95% CI, 0.12–0.32), but was also significant if initiated within 3 to 5 days after illness onset (adjusted HR 0.35; 95% CI, 0.21–0.58). In a subgroup of patients with respiratory failure, NAI treatment started within 5 days of illness shortened length of hospital stay by 2.0 days (95% CI, 0.27–3.7).¹

A 2014 meta-analysis of 9 double-blinded RCTs (N=4,328) compared a 5-day course of oral oseltamivir (75 mg every 12 hours) with placebo for treatment of seasonal influenza in adults with fever and at least 1 respiratory symptom (cough, sore throat, or coryza) and 1 constitutional symptom (headache, myalgia, sweats or chills, or fatigue).² Total follow-up was 21 days.

Oseltamivir resulted in a 21% shorter duration of symptoms than placebo in populations with confirmed influenza (time ratio 0.79; 95% CI, 0.74–0.85). The median duration of symptoms was 97.5 hours for oseltamivir and 122.7 hours for placebo (mean difference 25.2 hours; 95% CI, 16.0–36.2). After 48 hours of treatment with oseltamivir, lower respiratory tract complications requiring antibiotics were reduced compared with placebo (risk ratio [RR] 0.56; 95% CI, 0.42–0.75), with less risk of admission to a hospital for any cause (RR 0.37; 95% CI, 0.17–0.81).²

A double-blinded RCT of primarily low-income patients in Bangladesh assessed reduction of symptom duration with oseltamivir in 1,190 influenza patients, 80% of whom were 10 years old or younger.³ Influenza signs and symptoms were classified as major (eg, fever, dyspnea, mental status changes, lethargy) and minor (eg, cough, sore throat, headache, rhinorrhea).

When evaluated based on time of enrollment, treatment with oseltamivir 2 times daily (dosing not specified) for 5 days resulted in shorter duration of major symptoms by 1 day compared with placebo (hazard ratio [HR] 0.87; 95% CI, 0.79–0.95). However, when based on timing of initiation of treatment, the difference was not statistically significant. The presence of residual symptoms in patients (eg, rhinorrhea, nighttime cough, or wheeze) after the major signs had resolved was reduced in the oseltamivir group for all participants, regardless of time of enrollment compared with placebo (19% vs 26%; P=.01).³

**REFERENCES**

We invite your questions and feedback. Email us at EBP@fpin.org.
Is uncontrolled psoriasis a risk factor for cardiovascular disease?

**EVIDENCE-BASED ANSWER**

A patient with severe psoriasis is at increased risk of developing and dying from cardiovascular disease (CVD) (SOR: B, meta-analyses of cohort studies with significant heterogeneity).

A 2013 meta-analysis of 14 cohort studies from North America, Europe and Taiwan evaluated whether severe psoriasis (requiring systemic therapy or hospitalization) is a risk factor for CVD mortality and myocardial infarction (MI).¹ Sample sizes varied widely, with most studies comparing an age-matched unexposed cohort from the general population. The methods and extent of follow-up reporting were highly varied as well.

CVD mortality was increased in individuals with severe psoriasis compared with the general population (4 trials, n=42,518; standardized mortality ratio [SMR] 1.4; 95% CI, 1.2–1.6). A fifth study also found an increase in CVD mortality (n=3,603; hazard ratio [HR] 1.6; 95% CI, 1.3–2.0). No difference was noted in the incidence of MI in patients with severe psoriasis versus the general population (2 trials, n=6,458; HR 3.0; 95% CI, 0.7–14). Of note, significant heterogeneity was noted for all outcomes in this meta-analysis, and relevant confounding factors were incompletely addressed.¹

A 2013 meta-analysis of 9 cohort studies from Europe and Taiwan (6 of 9 also used in the preceding reference) from 6 countries (N=218,654) studied the risk of CVD mortality and MI for both mild and severe psoriasis compared with the general population over a mean follow-up of 2.7 to 22 years.² All but 1 study differentiated severe psoriasis as extent of disease requiring phototherapy, systemic medications, or inpatient hospitalization.

Severe psoriasis was associated with a significantly increased risk of CVD mortality (4 trials, n=16,591; risk ratio [RR] 1.4; 95% CI, 1.1–1.7) and MI (3 trials, n=7,048; RR 1.7; 95% CI, 1.3–2.2).²

A 2013 meta-analysis of 27 cohort and other observational studies (including 4 from the preceding references) investigated the risk of overall CVD (MI, angina, or coronary disease) in psoriasis (N=503,686 cases; including both “skin” psoriasis and psoriatic arthritis) compared with controls (N=29,686,694).³ Severity of psoriatic disease was not considered and mean study length was not provided.

Patients with psoriasis were more likely to have CVD (odds ratio [OR] 1.4; 95% CI, 1.2–1.7). The association was strongest in the studies of hospital-based patients (22 trials, n=270,310 cases and N=19,777,018 controls; OR 1.8; 95% CI, 1.4–2.4).³

**What are appropriate initial tests when evaluating a patient for possible pheochromocytoma?**

**EVIDENCE-BASED ANSWER**

The most accurate initial test for suspected pheochromocytoma is plasma-free metanephrines, with a sensitivity of 94% to 99% and a specificity of 89% to 96% (positive likelihood ratio [LR+] 9–23, negative likelihood ratio [LR–] 0.01–0.067) (SOR: A, diagnostic cohort studies and practice guideline).

A 2013 diagnostic study in a mixed population of volunteer reference patients without pheochromocytoma and patients previously tested for pheochromocytoma, established reference ranges and examined the accuracy of plasma-free metanephrines in the diagnosis of pheochromocytoma.¹ The reference populations included 116 children, 317 normotensive adults, 258 hypertensive adults, and 535 patients with a previously negative evaluation for pheochromocytoma. The test...
was validated in a separate group of 3,888 patients undergoing evaluation for pheochromocytoma, of whom 558 had confirmed disease by imaging or pathology and the others had no signs of tumor and were presumed to not have pheochromocytoma. The gold standard was pheochromocytoma diagnosed by pathology or imaging evidence of metastatic disease. The resulting data optimized cutoff values for plasma-free metanephrines (normetanephrine and metanephrine) that increased the diagnostic accuracy of testing for pheochromocytoma and reduced false-positive rates.

Use of fixed upper cutoffs for both normetanephrine (0.706 nmol/L) and metanephrine (0.325 nmol/L) yielded a diagnostic sensitivity of 93.9% and a specificity of 88.3% for patients in the validation population. Using an optimized curvilinear model, upper cutoffs for normetanephrine increased curvilinearly from 0.540 nmol/L for a 5-year-old to 1.415 nmol/L for a 75-year-old. Using the curvilinear model, plasma-free metanephrines had a sensitivity of 93.6% and a specificity of 96.0% for the diagnosis of pheochromocytoma, corresponding to an LR+ of 23.4 and an LR− of 0.067. Blood samples for the reference population were drawn under specific conditions (supine position, no caffeine for 24 hours, no acetaminophen for 5 days) and the reference values, sensitivity, and specificity may be valid only under these conditions.¹

In 2002, a multicenter cohort study evaluated the accuracy of plasma and urinary metanephrines in diagnosing pheochromocytoma.² The cohort included 214 patients with pheochromocytoma confirmed by pathology or evidence of metastatic disease and 644 patients without pheochromocytoma based on imaging or clinical follow-up. Using established upper reference limits (0.6 nmol/L for normetanephrine and 0.3 nmol/L for metanephrine), plasma-free metanephrines had a sensitivity of 99% (95% CI, 96%–100%) and a specificity of 89% (95% CI, 87%–92%), with an LR+ of 9 and an LR− of 0.01. Urinary fractionated metanephrines had a sensitivity of 97% (95% CI, 92%–99%) and a specificity of 69% (95% CI, 64%–72%), with an LR+ of 3.1 and an LR− of 0.04. The study analysis noted that plasma concentrations of normetanephrine higher than 2.19 nmol/L and metanephrine higher than 1.20 nmol/L confirm pheochromocytoma in 79% of patients with the tumor with no false positives. Plasma-free metanephrines and urinary fractionated metanephrines were more sensitive than plasma catecholamines, urinary catecholamines, urinary total metanephrines, and urinary vanillylmandelic acid (sensitivities ranging from 77% to 92%).

A 2014 review article referenced 78 different studies, guidelines, and other reviews, including the 2 studies mentioned above, and concluded that plasma-free metanephrines can exclude almost all cases of pheochromocytoma/paraganglioma based on the data from the cohort study above (sensitivity 99%, specificity 89%; LR+ 9, LR− 0.01).³ The review also recommended that urine fractionated metanephrines are appropriate for initial screening in nonspecialized centers, as the sensitivity of this test comes close to the value for plasma metanephrines (97%), although specificity is only 69% (LR+ 3.1, LR− 0.04).

The Endocrine Society released a clinical practice guideline in 2014 recommending that initial biochemical testing for pheochromocytoma should include measurements of plasma-free or urinary fractionated metanephrines.⁴

In children with mild persistent asthma, is “as needed” use of inhaled steroids as effective as daily inhaled steroids?

**EVIDENCE-BASED ANSWER**

The effectiveness of “as needed” and daily dosing of inhaled corticosteroids (ICS) for preventing exacerbations (requiring oral steroids), emergency room visits, or hospitalizations is no different, but there are 7% fewer symptomatic days with daily ICS use (SOR: B, systematic review of RCTs).

A systematic review identified 2 RCTs of preschool-aged and 2 of school-aged children (N=835) that compared intermittent versus daily ICS in patients with confirmed or

---

suspected persistent asthma.¹ Preschool-aged children (12–53 months old) with recurrent wheezing received daily budesonide 500 mcg or beclomethasone 400 mcg twice daily compared with intermittent ICS use for 1 to 2 weeks during exacerbations.

No statistically significant difference was noted between the interventions for exacerbations requiring steroids at 12 to 52 weeks follow-up (2 RCTs, n=498; 28% vs 25%; relative risk [RR] 1.1; 95% CI, 0.85–1.4). In school-aged children (5–15 years old) with symptomatic mild persistent asthma not currently using ICS, daily use of inhaled budesonide ranging from 100 to 500 mcg beclomethasone per day was compared with its use only during exacerbations. No difference was noted between the interventions for exacerbations requiring steroids at 12 to 44 weeks follow-up (2 RCTs, n=329; 22% vs 22%; RR 1.3; 95% CI, 0.84–1.9).¹

Individual pediatric studies showed no statistically significant difference in emergency department visits or hospitalizations, but did favor daily ICS over intermittent ICS in mean number of symptomatic days (2 trials, n=214; mean difference [MD] –7% days; 95% CI, –14% to –1%) and proportion of asthma control days (3 trials, n=330, MD –9%; 95% CI, –14% to –4%). A statistically significant difference was noted in change of height from baseline favoring intermittent ICS use (4 trials, n=532; MD 0.41 cm; 95% CI, 0.13–0.69). Limitations of the studies include underpowered sample sizes and short follow-up of a year or less.¹

In children with mild persistent asthma, the National Heart, Lung, and Blood Institute’s National Asthma Education and Prevention Program evidenced-based guidelines from 2007 recommends initiating a low-dose daily ICS as first-line treatment based on strong evidence from RCTs, and does not consider intermittent dosing as an option.²

In pregnant women undergoing induction with misoprostol, is vaginal or oral dosing better?

**EVIDENCE-BASED ANSWER**

Vaginal and oral misoprostol are comparable in pregnant women undergoing third trimester induction of labor as far as the outcomes of vaginal delivery not achieved in 24 hours, caesarean section, serious neonatal morbidity or perinatal death, and serious maternal morbidity or death. Vaginal misoprostol is associated with higher rates of postpartum hemorrhage and lower 5-minute Apgar scores than oral (SOR: B, based on systematic review of quality RCTs). The World Health Organization (WHO) recommends either low-dose vaginal or oral misoprostol for induction of labor at term for women who have not had a previous cesarean section; while the American Congress of Obstetricians and Gynecologists (ACOG) recommends oral over vaginal misoprostol (SOR: C, evidence-based guidelines).

A 2014 Cochrane review of 37 RCTs (N=6,417) assessed the efficacy of oral misoprostol for labor induction in women who required third trimester induction with a viable fetus compared with vaginal misoprostol.¹ Primary outcomes included vaginal delivery not achieved in 24 hours, uterine hyperstimulation with fetal heart rate changes, caesarean section, serious neonatal morbidity or perinatal death, and serious maternal morbidity or death.

At lower doses of oral misoprostol (25 mcg), the incidence of uterine hyperstimulation was similar to vaginal misoprostol (25–100 mcg) (risk ratio [RR] 0.30; 95% CI, 0.07–1.2), but higher oral doses of misoprostol (200 mcg) were associated with increased risk of hyperstimulation than vaginal misoprostol (25–100 mcg) (RR 1.6; 95% CI, 1.1–2.4). No significant differences were seen in the rates of caesarean section (RR 0.93; 95% CI, 0.81–1.1), serious neonatal morbidity/death (RR 0.80; 95% CI, 0.60–1.3), serious maternal morbidity/death (RR 2.0; 95% CI, 0.19–20.9), or rates of vaginal delivery not achieved in 24 hours (RR 1.1; 95% CI, 0.86–1.4). Oral misoprostol was associated with a reduction in low Apgar score at 5 minutes (RR 0.60; 95% CI, 0.44–0.82), lower rates of postpartum hemorrhage


Is progesterone an effective treatment for preventing miscarriage in unexplained recurrent pregnancy loss?

**EVIDENCE-BASED ANSWER**

Progesterone reduces the odds of miscarriage for women who have experienced 3 or more consecutive pregnancy losses (odds ratio [OR] 0.39) compared with placebo, but does not alter outcomes in women with 1 or 2 prior unexplained miscarriages (SOR: B, meta-analysis of small RCTs). An older report from the Royal College of Obstetricians and Gynaecologists (RCOG) found insufficient evidence to assess the effect of progesterone and did not recommend any empiric treatment of recurrent pregnancy loss (SOR: C, expert opinion).

A 2013 systematic review and meta-analysis of 14 RCTs (N=1,458) studied both the efficacy of progesterone to prevent miscarriage in the general population and any adverse events associated with its use.¹ Trials included women with no history of miscarriage and women with recurrent miscarriages. In trials that exclusively enrolled women with a history of pregnancy loss, the losses were all unexplained. Women were randomized to progesterone (oral, intramuscular, intravaginal, implant) or placebo; however, in some trials the controls received no treatment. A multitude of progesterone formulations and schedules were used. The primary outcome was miscarriage. The secondary outcomes for mothers were severity of morning sickness, thrombotic events, depression, admission to special care unit, and subsequent fertility. Secondary outcomes for babies were preterm birth, stillbirth, neonatal death, birth weight less than 2,500 g, genital abnormalities, teratogenic effects, and admission to special care unit.

Progesterone did not reduce the odds of miscarriage in the general population (14 trials, n=1,458; OR 0.99; 95% CI, 0.78–1.2) or in women with 2 or more pregnancy losses (10 trials, n=450; OR 0.68; 95% CI, 0.43–1.1). Progesterone did reduce the odds of miscarriage in women with 3 or more consecutive pregnancy losses (4 trials, n=225; OR 0.39; 95% CI, 0.21–0.72). No significant differences were noted in the secondary outcomes between the 2 groups. The funnel plot showed no evidence of publication bias, and the overall

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quality of the evidence was described as “moderately
good.”¹

The 2011 RCOG guideline for the treatment of recurrent
first- and second-trimester pregnancy loss stated that there
is insufficient evidence to assess the effect of progesterone
on recurrent pregnancy loss (Grade B recommendation
with 1+ evidence – extrapolation from well-conducted meta-
analyses).² Their recommendation was based on a 2008
Cochrane review, which did not include a large study directly
addressing this issue. In the group’s closing expert opinion,
RCOG stated that all empiric treatment in unexplained
recurrent pregnancy loss was unnecessary and should be
avoided.

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   (10):CD003511.[STEP 1]
2. Royal College of Obstetricians and Gynaecologists (RCOG). The investigation and treatment of
couples with recurrent first-trimester and second-trimester miscarriage. Green Top Guideline 17.
London, UK: RCOG; 2011.[STEP 1]

LETTER TO
THE EDITOR

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

I read with interest the HelpDesk Answer article in the
October 2016 issue of Evidence-Based Practice
(2016;19[10]:10) about regional anesthesia and childbirth
outcomes. I am concerned that reference 2 (Simmons SW,
et al. Cochrane Database Syst Rev. 2012;[10]:CD003401) was
not fully described and hence the final clinical
recommendations of the HelpDesk Answer may have been
misleading.

This meta-analysis was a 3-way comparison: combined
spinal-epidural (CSE), low-dose epidural, and traditional
(high-dose) epidural—this last a form of anesthesia rarely
used these days. Simmons et al concluded that there was
no advantage to CSE compared with low-dose epidural, the
current standard. Your HelpDesk Answer article, in contrast,
does not describe the outcome of the low-dose epidural
arm, and focused on the lower risk of instrumental delivery
with CSE than with the traditional epidural.

I do not think the evidence supports counseling patients
to opt for a CSE specifically to avoid an instrumental delivery.
Simmons et al actually suggests that commonly used low-
dose epidurals do not increase the instrumental delivery
rate, compared with CSE.

Marianna Crowley, MD

Editor’s reply
Thank you for writing. Upon further review, the
authors of the HelpDesk Answer (Collin Musa, MD,
and Ashley Hildebrand, MD) agreed with Dr. Crowley’s
conclusion regarding Simmons et al. The evidence in
that Cochrane review does not support counseling
patients to have a CSE rather than a low-dose epidural
in order to avoid instrumental vaginal delivery. There
was no difference in instrumental vaginal rates when
comparing low-dose epidural with CSE. This was
indeed a more pertinent conclusion to be drawn from
the second meta-analysis.

Nevertheless, the evidence does suggest CSE is
superior to traditional epidural analgesia with regards
to this outcome.

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Do antiarrhythmic agents prevent sudden death in patients with heart failure?

**Bottom line**
Amiodarone and beta-blockers reduce sudden cardiac death (SCD) in a heterogeneous population of patients with heart failure (HF), acute myocardial infarction (AMI), and ventricular arrhythmias. However, only beta-blockers are associated with a reduction in all-cause mortality (SOR: **A**, meta-analyses of high-quality RCTs). In patients selected specifically for HF (NYHA class II and III), amiodarone has no effect on 5-year all-cause mortality and increases mortality in the subgroup of patients with just NYHA class III congestive heart failure (CHF) (SOR: **B**, single high-quality RCT). Implantable cardioverter defibrillators (ICDs) reduce all-cause mortality in HF patients and are better tolerated than amiodarone (SOR: **B**, high-quality RCT).

**Evidence summary**
A 2013 meta-analysis of 30 RCTs (N=24,779) compared beta-blockers with placebo for SCD prevention in patients with CHF, including NYHA class II-IV CHF, ischemic dilated cardiomyopathy, AMI, and combinations thereof.¹ Most studies used oral metoprolol 150 mg, carvedilol 50 mg, or bisoprolol 5 to 10 mg daily for more than 30 days in patients with mean ages ranging from 28 to 76 years. Beta-blockers reduced SCD compared with placebo (odds ratio [OR] 0.69; 95% CI, 0.62–0.77; number needed to treat [NNT]=43). Beta-blockers decreased cardiovascular death (CVD) (OR 0.71; 95% CI, 0.64–0.79; NNT=26) and all-cause mortality (OR 0.67; 95% CI, 0.59–0.76; NNT=21) compared with placebo.¹

A 2009 meta-analysis of 15 RCTs (N=8,522) compared oral amiodarone 200 to 400 mg daily for more than 30 days with placebo for the prevention of SCD in patients with cardiomyopathy, defined as NYHA class II-IV CHF, AMI, frequent premature ventricular contractions, nonsustained ventricular tachycardia, ejection fraction (EF) <40%, or a combination thereof.² Mean patient age ranged from 57 to 68 years and all included studies contained at least 65% men. Altogether, 715 SCDs occurred. The odds of SCD with amiodarone was significantly less than with placebo (OR 0.71; 95% CI, 0.61–0.84; NNT=38).

Amiodarone also reduced CVD compared with placebo (OR 0.82; 95% CI, 0.71–0.94). Neither all-cause mortality nor CHF death reached statistical significance with amiodarone compared with placebo. The most common toxicities associated with amiodarone versus placebo were thyroid (3.6% vs 0.4%; OR 5.7; 95% CI, 2.9–11.0) and pulmonary (2.9% vs 1.5%; OR 2.0; 95% CI, 1.3–3.0) issues. Therapy discontinuation occurred in 32% patients taking amiodarone and 21% taking placebo in the 9 studies reporting discontinuation rates.²

A 2005 randomized, double-blind multicenter trial (N=2,521) investigated all-cause mortality in patients with a median age of 60 years with NYHA class II or III CHF and EF ≤35% receiving conventional therapy and placebo, amiodarone, or a shock-only, single-lead ICD.³ Conventional therapy included a beta-blocker, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, diuretic, aspirin, digoxin, or statin when indicated. Amiodarone patients were loaded with 800 mg daily for 1 week, 400 mg daily for 3 weeks, then 200 to 400 mg daily based on body weight. Compared with placebo, ICD therapy decreased 5-year, all-cause mortality (hazard ratio [HR] 0.77; 97.5% CI, 0.62–0.96) while amiodarone did not (HR 1.1; 97.5% CI, 0.86–1.3). Subgroup analysis revealed ICD therapy did not reduce mortality compared with placebo in NYHA class III CHF (HR 1.2; 96.5% CI, 0.84–1.6), but it did in class II CHF (HR 0.54; 97.5% CI, 0.40–0.74). Amiodarone increased mortality in class III CHF (HR 1.4; 97.5% CI, 1.1–2.0). Discontinuation rates were 4% for ICD and 32% for amiodarone related to increased tremor, hypothyroidism, and unspecified reasons.³

**REFERENCES**

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What is the best treatment for REM sleep behavior disorder (RBD)?

**EVIDENCE-BASED ANSWER**

In patients with RBD, melatonin decreases the amount of REM sleep without atonia and improves subjective symptom scores (SOR: C, single small RCT). Clonazepam and melatonin are associated with reduced REM sleep behaviors and injuries (SOR: C, single descriptive survey). A bed alarm may prevent injury in patients with medication-refractory RBD (SOR: C, small case series).

Normal REM sleep is associated with temporary skeletal muscle atonia. RBD is characterized by an increased amount of REM sleep without atonia (RSWA), resulting in potentially injurious dream enactment behaviors.

A 2010 double-blind, randomized, placebo-controlled, crossover study (N=8) compared the effects of 3 mg oral melatonin daily versus placebo on percentage of RSWA and clinical global impression in men with RBD.¹ A clinical global impression score was used to assess the severity of mental health symptoms and therapeutic response on a scale of 1 to 7. Higher scores signified more severe illness.

Melatonin therapy for 4 weeks was associated with a significant reduction in the mean percentage of REM sleep characterized as RSWA (39% at baseline vs 27% posttreatment; \( P = .012 \)). The clinical global impression scale was also improved with melatonin treatment (6.1 at baseline vs 4.6 posttreatment; \( P = .024 \)). Placebo therapy was not associated with significant improvement in either RWSA percentage (39% at baseline vs 31% posttreatment; \( P = .102 \)) or clinical global impression scoring (6.1 at baseline vs 5.6 posttreatment; \( P = .208 \)). The study included patients receiving antidepressant medications known to exacerbate RBD.¹

A 2013 prospective, survey-based study evaluated 45 adult patients treated for RBD between 2008 and 2010 at the Mayo Clinic using oral melatonin (n=25), clonazepam (n=18), or both (n=2).² Patients and bed partners or family members were asked to rate pre- and posttreatment dream enactment behaviors, falls, and injuries on a 0 to 10 visual analog scale (VAS), with 10 corresponding to more frequent and severe events.

Significant differences between pre- and posttreatment RBD VAS ratings were seen for both melatonin (n=27; 6.7 vs 4.2; \( P = .0001 \)) and clonazepam (n=20; 6.5 vs 4.2; \( P = .0005 \)). Median effective doses of melatonin and clonazepam were 6 and 0.5 mg, respectively.²

A small case series evaluated customized bed alarm use in 4 patients with RBD refractory to treatment with both oral clonazepam and melatonin.³ The bed alarms used recordings of calming messages from family members triggered by significant sleep movements.

REM sleep events (near, minor, and serious injuries) decreased from 4.2 per patient per month pretreatment to 0.05 per patient per month posttreatment. No statistical tests were reported. Study limitations included small sample size and lack of generalizability to patients with medication-responsive RBD.³

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Do adults previously vaccinated with the shingles vaccine need a booster?

**EVIDENCE-BASED ANSWER**

The answer is unclear. The shingles vaccine has been shown to reduce the severity and incidence of shingles for 5 years and the incidence of postherpetic neuralgia (PHN) for 2 years after vaccination (SOR: B, based on a single RCT and follow-on study). Its effectiveness beyond those timeframes is less certain, and there are currently no studies assessing the safety or efficacy of a booster (SOR: C, consensus guideline).

A 2005 double-blind RCT with 38,546 patients evaluated whether the shingles vaccine decreased the incidence and severity of shingles and PHN.¹ Participants were immunocompetent, older than 60, and had a history of chicken pox or had lived in the United States for 30 years. The intervention group received a single vaccination and the control group received a placebo injection. Disease severity was measured by a duration-severity index called “burden of illness” (BOI), calculated as the area under the curve of patient self-reported worst zoster pain plotted against time during the 182-day period after the onset of rash. Subjects who did not develop shingles or did not have pain received a score of zero. Vaccine efficacy (VE) was defined as the reduction of BOI in the vaccine group compared with the control group (VE=1 – relative risk).

Over a median of 3 years, the vaccine group showed a reduction in the severity of shingles (VE<sub>BOI</sub>: 61%; 95% CI, 51–69) and a reduction in the incidence of shingles (VE<sub>INC</sub>: 51%; 95% CI, 44–58%) and PHN (VE<sub>INC</sub>: 67%; 95% CI, 48–79). Based on this evidence, the CDC’s Advisory Committee on Immunization Practices (ACIP) recommended 1 dose of the shingles vaccine in adults older than 60 years.¹

A 2015 follow-on study used a subset of the above study’s vaccinated participants (N=6,867) who were compared with a computer-generated control group, as most nonvaccinated subjects were vaccinated by that point.² The aim of this study was to extend the primary and secondary objectives out to 11 years postvaccination. Participants were 97.8% Caucasian and 64 to 95 years old.

The **TABLE** shows vaccine efficacy data by year out to 11 years postvaccination. When comparing disease severity, there was a reduction in the vaccine group out to 5 years,

<table>
<thead>
<tr>
<th>Years postvaccination</th>
<th>Vaccine efficacy for disease severity</th>
<th>Vaccine efficacy for incidence of PHN</th>
<th>Vaccine efficacy for incidence of shingles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>79.2% (66.8–86.9)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>83.4% (56.7–95.0)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62.0% (49.6–71.6)&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Year 2</td>
<td>54.9% (32.0–70.3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69.8% (27.3–89.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48.9% (34.7–60.1)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Year 3</td>
<td>44.4% (17.6–62.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38.3% (–44.7 to 75.0)</td>
<td>46.8% (31.1–59.2)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Year 4</td>
<td>66.9% (37.5–82.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60.7% (–36.3 to 91.0)</td>
<td>44.6% (20.5–61.8)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Year 5</td>
<td>74.9% (48.6–87.7)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>73.8% (–37.8 to 97.3)</td>
<td>43.1% (5.1–66.5)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Year 6</td>
<td>23.6% (–58.1 to 63.1)</td>
<td>32.0% (–100 to 87.3)</td>
<td>30.6% (–6.0 to 54.6)</td>
</tr>
<tr>
<td>Year 7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>47.7% (20.9–65.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26.3% (–40.0 to 66.3)</td>
<td>46.0% (28.4–60.2)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Year 8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>46.2% (25.8–61.0)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27.5% (–37.5 to 66.9)</td>
<td>31.1% (11.2–47.6)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Year 9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>27.6% (4.5–45.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60.5% (7.7–87.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.8% (–16.5 to 26.4)</td>
</tr>
<tr>
<td>Year 10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33.3% (1.5–54.8)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44.2% (–21.5 to 79.5)</td>
<td>14.1% (–11.3 to 34.9)</td>
</tr>
<tr>
<td>Year 11&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.9% (–48.6 to 42.9)</td>
<td>11.5% (–100 to 81.7)</td>
<td>–1.7% (–57.1 to 37.9)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Significant results.

<sup>b</sup>Computer-generated placebo groups.

PHN=postherpetic neuralgia.
but not to 6 years when using a human control group. When using a computer-generated control group there was a reduction again seen from year 7 to 10, but not 11. When comparing the incidence of PHN there was a reduction in the vaccine group during the first 2 years postvaccination.²

In 2014, the ACIP released a statement updating their stance in light of these new data and maintained their original recommendation of 1 dose of the shingles vaccine at age 60.³ The rationale for not recommending a booster included uncertain duration of vaccine protection, uncertain cost-effectiveness, uncertain vaccine booster timing for greatest reduction in disease burden, and a lack of studies investigating the need for revaccination.

**Evidence-Based Practice**

**HELPDESK ANSWERS**

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


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**Does vitamin D supplementation in elderly adults improve cognitive outcomes?**

**EVIDENCE-BASED ANSWER**

Vitamin D supplementation for elderly adults is associated with improvements in some measures of cognition and executive function (SOR: **B**, low-quality cohort studies). Pooled results of studies including both older and younger patients show vitamin D repletion is associated with moderate improvements in executive function compared with baseline but not compared with controls (SOR: **B**, meta-analysis of cohort studies and RCT).

A 2013 meta-analysis (1 RCT, 2 cohort, and 14 observational studies) examined the association between hypovitaminosis D and cognitive functioning and the effect of vitamin D supplementation.¹ In the supplementation studies, the patients were a heterogeneous group of young adults, and community- and nursing home-dwelling elderly with baseline vitamin D levels ranging from 16 to 31 ng/mL. Executive functions and assessment methods included global functioning assessed with the clock drawing test (CDT) and frontal assessment battery (FAB), the ability to move from 1 cognitive operation to another with the switch-cost reaction time (SCRT), the ability to inhibit an automatic response with the stop-signal reaction time (SSRT), and information updating with the 2-back task.

Meta-analysis of 3 supplementation studies (2 cohort, 1 RCT; n=491) demonstrated that vitamin D supplementation (800 IU/d to 50,000 IU 3 times per week) moderately improved executive functions (effect size [ES] −0.50; 95% CI, −0.69 to −0.32) compared with baseline, but resulted in no difference compared with control (ES 0.14; 95% CI, −0.04 to 0.32). Overall, 2 of 3 interventional studies mentioned above included the geriatric population and are described below. Limitations of the interventional studies included control groups with high baseline vitamin D concentrations (29–35 ng/mL).¹

A 2012 retrospective cohort study examined the association between vitamin D and cognition.² Outpatients (n=44) without recent vitamin D supplementation and no prescription for antidementia drugs who visited the University Memory Centre of Agnes, France, twice between June 2009 and October 2011 were included in the cohort study (median age 80 years, 55% female, 100% Caucasian). Global cognitive function was assessed at baseline and follow-up visits using the Mini-Mental State Examination (MMSE; total score 30) and the Cognitive Assessment Battery (CAB; total score 96). Executive functions were assessed using the Frontal Assessment Battery (FAB; total score 18). The 20 patients in the intervention group received vitamin D3 supplements (800 IU/d or 100,000 IU/month) and 24 patients served as controls and received no supplementation.

No difference was noted between vitamin D3 and control groups on baseline cognitive scores or serum vitamin D concentration (control group: 63 ng/dL, vitamin D3 group: 42 ng/dL). After 16 months of follow-up, the vitamin D3 group had higher 25OHD levels (75 ng/dL; *P*=.001) than at baseline and higher than the control group (48 ng/dL; *P*<.001). In the vitamin D3 group, the MMSE improved by a mean of 1 point, CAB by 2 points, and the FAB by 1 point, while the control
A 2008 prospective cohort study of 63 nursing home residents (73% women, mean age 87 years) evaluated the effect of vitamin D supplementation on cognitive function. In total, 25 residents received oral vitamin D2 supplements (50,000 IU 3 times per week) for 4 weeks. The control group received no supplementation. The mean vitamin D level at baseline was 17 ng/mL in the supplementation group and more than 30 ng/mL after 4 weeks of treatment (P < .001), while the control group was 35 ng/mL at baseline and remained unchanged at follow up.

After 4 weeks, no differences were noted between the vitamin D2 group and the control group on results of the timed walk test (4-meter gait time), the 12-question neuropsychiatric inventory, animal fluency (number of animals named in 60 seconds), or the clock drawing test.³

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What are the best office-based brief screening tools for identification of possible dementia?

EVIDENCE-BASED ANSWER

The MMSE, SPMSQ, FCSRT, 7MS, TICS, IQCODE, 6CIT, AMT, GPCOG, Mini-Cog, MIS, MoCA, STMS, mMMSE, SAS-Si, and SLUMS all have sensitivity and specificity >80% and have been validated in the primary care setting (SOR: A, 2 systematic reviews).

A 2013 systematic review and meta-analysis of 55 diagnostic accuracy studies (N=25,992) examined the test performance of screening instruments to detect cognitive impairment in elderly, community-dwelling primary care patients.¹ To be included in the review, diagnostic accuracy studies of screening tests had to compare the index test with a reference standard (eg, clinical assessment or neuropsychological testing, with explicit diagnostic criteria). Twelve tools were validated in primary care–relevant populations in fair- to good-quality studies. Multiple instruments had sensitivity and specificity >80% (see TABLE 1).

The Mental Status Questionnaire and the Verbal/Category Fluency Tests performed below the others in the group. The 6-Item Screener, Visual Association Test, General Practitioner Assessment of Cognition, Activities of Daily Living/Instrumental Activities of Daily Living, Benton Orientation Test, Delayed Recall Test, and Short Concord Informant Dementia Scale all had more than 80% sensitivity and specificity to detect dementia in a single study, but their test performance had not been reproduced in other primary care–relevant populations.¹

A 2014 systematic review of 12 review articles and 2 diagnostic accuracy studies examined the test performance of screening instruments to detect cognitive impairment in the primary care setting.² Total N was not provided. The review revealed no single screening study with superior sensitivity and specificity. Multiple screening tools were found to have sensitivities and specificities >80% across multiple studies (see TABLE 2).

When considering factors such as application time, sensitivity, specificity, and number of studies, the authors recommended 6CIT, AMT, GPCOG, Mini-Cog, MIS, MoCA, and STMS as possible alternatives to MMSE for screening in the primary care setting.² The authors did not define specific criteria for these recommendations.


### TABLE 1

**Screening tools for dementia as reviewed by Lin et al**

<table>
<thead>
<tr>
<th>Screening tool</th>
<th>Number of trials</th>
<th>N</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7MS: 7 Minute Screen</td>
<td>2</td>
<td>553</td>
<td>100</td>
<td>95–100</td>
</tr>
<tr>
<td>MIS: Memory Impairment Screen</td>
<td>5</td>
<td>1,971</td>
<td>43–86</td>
<td>93–97</td>
</tr>
<tr>
<td>AMT: Abbreviated Mental Test</td>
<td>4</td>
<td>824</td>
<td>42–92</td>
<td>93–95</td>
</tr>
<tr>
<td>SPMSQ: Short Portable Mental Status Questionnaire</td>
<td>4</td>
<td>1,057</td>
<td>92–100</td>
<td>84–100</td>
</tr>
<tr>
<td>TICS: Telephone Interview for Cognitive Status</td>
<td>2</td>
<td>677</td>
<td>74–88</td>
<td>86–87</td>
</tr>
<tr>
<td>MMSE: Mini-Mental State Exam</td>
<td>24</td>
<td>10,185</td>
<td>88</td>
<td>84</td>
</tr>
<tr>
<td>IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly</td>
<td>5</td>
<td>1,108</td>
<td>75–88</td>
<td>65–91</td>
</tr>
<tr>
<td>Mini-Cog</td>
<td>4</td>
<td>1,570</td>
<td>76–100</td>
<td>54–85</td>
</tr>
</tbody>
</table>

### TABLE 2

**Screening tools for dementia as reviewed by Yokomizo et al**

<table>
<thead>
<tr>
<th>Screening tool</th>
<th>Number of trials</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV, range</th>
<th>NPV, range</th>
<th>Time for administration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7MS: 7 Minute Screen</td>
<td>5</td>
<td>89–95</td>
<td>94–99</td>
<td>0.82–1.00</td>
<td>0.75–0.97</td>
<td>7</td>
</tr>
<tr>
<td>MIS: Memory Impairment Screen</td>
<td>9</td>
<td>74–86</td>
<td>96–97</td>
<td>0.48–0.82</td>
<td>0.92</td>
<td>4</td>
</tr>
<tr>
<td>AMT: Abbreviated Mental Test</td>
<td>6</td>
<td>73–100</td>
<td>71–100</td>
<td>0.23–0.63</td>
<td>0.92–1.00</td>
<td>3–6</td>
</tr>
<tr>
<td>SPMSQ: Short Portable Mental Status Questionnaire</td>
<td>5</td>
<td>55–86</td>
<td>79–96</td>
<td>No data</td>
<td>No data</td>
<td>3–6</td>
</tr>
<tr>
<td>MMSE: Mini-Mental State Exam</td>
<td>8</td>
<td>69–91</td>
<td>87–99</td>
<td>0.40–0.91</td>
<td>0.71–0.94</td>
<td>5–12</td>
</tr>
<tr>
<td>mMMSME: modified Mini-Mental State Examination</td>
<td>3</td>
<td>83–94</td>
<td>85–90</td>
<td>No data</td>
<td>No data</td>
<td>12–15</td>
</tr>
<tr>
<td>6CIT: 6 Item Cognitive Impairment Test</td>
<td>5</td>
<td>79–83</td>
<td>77–100</td>
<td>1.00</td>
<td>0.74–0.90</td>
<td>4–10</td>
</tr>
<tr>
<td>GPCOG: General Practitioner assessment of Cognition</td>
<td>9</td>
<td>82–85</td>
<td>83–86</td>
<td>0.61–0.80</td>
<td>0.92</td>
<td>4–5</td>
</tr>
<tr>
<td>Mini-Cog</td>
<td>9</td>
<td>76–99</td>
<td>89–96</td>
<td>0.27–0.41</td>
<td>0.92</td>
<td>2–4</td>
</tr>
<tr>
<td>MoCA: Montreal Cognitive Assessment</td>
<td>5</td>
<td>100</td>
<td>87</td>
<td>No data</td>
<td>No data</td>
<td>10–15</td>
</tr>
<tr>
<td>STMS: Short Test of Mental Status</td>
<td>5</td>
<td>86–95</td>
<td>79–96</td>
<td>0.79–0.95</td>
<td>0.88–0.98</td>
<td>5</td>
</tr>
<tr>
<td>SAS-SI: Short And Sweet Screening Instrument</td>
<td>3</td>
<td>94</td>
<td>81–91</td>
<td>0.32–0.48</td>
<td>0.99–1.00</td>
<td>10</td>
</tr>
<tr>
<td>SLUMS: St. Louis University Mental Status Examination</td>
<td>3</td>
<td>100</td>
<td>81–98</td>
<td>No data</td>
<td>No data</td>
<td>7–10</td>
</tr>
</tbody>
</table>

NPV=negative predictive value; PPV=positive predictive value.
What is the efficacy of eccentric exercises for the treatment of patellar tendonitis?

**EVIDENCE-BASED ANSWER**

In patients with patellar tendonitis (jumper’s knee), eccentric training results in similar improvements in pain and function compared with normal training, corticosteroid injections, heavy slow resistance training, and surgery, but more improvement than concentric exercises, ultrasound, or friction (SOR: B, small RCTs).

A 2007 systematic review compared eccentric squat exercises (EE) with other interventions (concentric exercises [CE], pulsed ultrasound, friction, and normal training) on functional status, pain, and patient satisfaction on return to activity over 4 to 12 weeks in athletes 17 to 42 years old with patellar tendinopathy (4 RCTs, N=93).¹

Pain improved on a visual analog scale (VAS) scores (range 0–100, higher scores=more pain) favoring EE over CE (1 trial, n=15; weighted mean difference (WMD) 44.8 mm; 95% CI, 20.1–69.5). Another study (n=30) showed patients doing EE were more likely than those receiving ultrasound (relative risk [RR] 21; 95% CI, 1.4–31) or friction treatments (RR 5; 95% CI, 1.5–17) to rate their pain as “much better/no pain” versus “worse/no change/slightly better.” Two trials evaluated functional pain status using the Victorian Institute of Sport Assessment (VISA), an index of severity of symptoms in daily living and sporting activities (range 0–100, with 100 being symptom-free). One trial found improvement with EE versus CE at 12 weeks (n=15; WMD 45.9; 95% CI, 24.5–67.3), but another comparing EE with normal training did not find improvement (n=29; WMD 0.10; 95% CI, –14.38 to 14.58). Pooled data (2 trials, n=34) on satisfaction with return to activity was significantly better with EE than with CE at 12 weeks (RR 4.2; 95% CI, 0.08–206.4) and at a 33-month follow-up (RR 17.3; 95% CI, 1.2–260).¹

A 2009 single-blind RCT compared peritendinous corticosteroid injections (CORT), eccentric decline squat training (EE), and heavy slow resistance training (HSR) at baseline, 12 weeks, and 6 months on primary outcomes of function (VISA) and pain during activity (0–100 VAS).² Recreational male athletes (n=37) ages 18 to 53 years (mean age 32 years) had ultrasonography-confirmed chronic patellar tendinopathy. The CORT group received 2 injections of 40 mg methylprednisolone in 0.5 mL lidocaine 4 weeks apart. The EE group performed unilateral squats on a 25° decline board. The HSR group performed eccentric and concentric movements using bilateral squats, leg presses, and hack squats.

All 3 modalities improved function and decreased pain after 12 weeks, but there was no difference between groups (see TABLE 1).²

A 2006 RCT (N=35 patients) compared open patellar tenotomy (n=20 tendons) with eccentric strength training (EE) using 25° decline board squats (n=20 tendons) as measured by VISA scores and pain scores (0–10 VAS) at 3, 6, and 12 months in patients 19 to 49 years old with patellar tendinopathy.³

**TABLE 1**

<table>
<thead>
<tr>
<th>Function and pain scores in jumper’s knee treated with corticosteroid injections, eccentric exercises, or heavy slow resistance training²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosterone injection</strong> (n=12)</td>
</tr>
<tr>
<td>**0 week</td>
</tr>
<tr>
<td>Function (VISA score)</td>
</tr>
<tr>
<td>Pain (VAS)</td>
</tr>
</tbody>
</table>

Change from baseline to 12 weeks significant for all 3 groups (P<.05). Between-group differences were not significant.

VAS=visual analog scale (range 0–100, with 100 being worst pain); VISA=Victorian Institute of Sport Assessment (range 0–100, with 100 being symptom-free).
Mean VISA scores improved significantly in both the surgery and EE groups, from baseline scores of about 30 to 12-month scores of about 70, but no difference in scores was noted between groups. Pain scores improved significantly from baseline to 12 months in both surgery and eccentric groups for standing jump, counter-movement jump, and leg-press (see Table 2).³

**TABLE 2**

<table>
<thead>
<tr>
<th>Test</th>
<th>Surgery group</th>
<th>Eccentric training group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 Months</td>
</tr>
<tr>
<td>Standing jump</td>
<td>4.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Counter-movement jump</td>
<td>4.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Leg press</td>
<td>4.1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Mean pain scores on an 11-point visual analog scale: 0 no pain, 10 max pain. Change from baseline to 12 months significant for all tests in both groups (P<.5). Between-group differences were not reported.

**Does adenotonsillectomy decrease asthma attacks in children?**

**EVIDENCE-BASED ANSWER**

In children with asthma, adenotonsillectomy is associated with 30% fewer asthma exacerbations, less status asthmaticus, and fewer emergency room (ER)/urgent care visits and hospitalizations. Additionally, adenotonsillectomy is associated with improved asthma control test (ACT) scores and less asthma medication use (SOR: B, pre-post cohort and case-control studies).

A 2014 prospective cohort study evaluated 130 children (2–18 years old), 66 with and 64 without asthma, undergoing adenotonsillectomy at a single medical center for either primary tonsillar hypertrophy (75%) or tonsillitis/infection (23%).³ Primary outcomes included asthma control as measured on the ACT and medication usage and asthma-related healthcare utilization as measured by ER and urgent care visits. Parents completed the ACT and a questionnaire about the patient’s medication use and asthma-related healthcare utilization before and 6 months postsurgery. The ACT is a 25-point test (min score 5, max score 25) with a score <19 indicating less than adequate control.

Postadenotonsillectomy, mean ACT scoring significantly improved in the cohort with asthma and surgery (median increase from 22 points presurgery to 25 points postsurgery, P<.001). In the subgroup of children with poorly controlled asthma, there was greater

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improvement in the ACT score (median improvement of 6 points, \( P < .01 \)). ER and urgent care visits significantly decreased postadenotonsillectomy in the cohort with asthma and surgery (from 1.9 visits/year baseline to 0.40 visits/year postsurgery; \( P < .05 \)). Prescribed courses of oral corticosteroids significantly decreased in this same group (from 1.1 to 0.21 courses/year; \( P < .01 \)). Missed school days due to asthma were significantly decreased after surgery (3.9 to 1.1 missed days/year; \( P < .05 \)).¹

A 2014 retrospective cohort study of 13,506 children with asthma and adenotonsillectomy (AT+) were compared with an age-, sex-, geographic-, and home environment-matched cohort of 27,012 children with asthma without adenotonsillectomy (AT−) to evaluate if surgery was associated with asthma control.² Comparison was performed 1 year preop versus 1 year postop in AT+ versus AT− matches. Primary outcomes included occurrence of asthma exacerbation or status asthmaticus, with secondary outcomes of asthma-related ER visits, asthma-related hospitalizations, and asthma-related CPT codes and prescriptions.

Fewer asthma exacerbations occurred in the AT+ group than in the AT− group (relative risk reduction [RRR] 30.2% vs 2%; \( P < .0001 \)) as well as less status asthmaticus (RRR 37.9% vs 6.8%; \( P < .0001 \)). The AT+ group had fewer asthma-related ER visits (RRR 25.6% vs 0.0%; \( P < .0001 \)) and asthma-related hospitalizations (RRR 35.8% vs 12.2%; \( P = .0025 \)) in the year after adenotonsillectomy than the AT− group.²

A 2012 retrospective cohort study of 11,114 children in Belgium younger than 15 years, undergoing adenotonsillectomy for any reason between 2002 and 2003, evaluated respiratory medication use pre- and postsurgery.³ Of patients studied, 4,654 used respiratory medication before the surgery. The primary outcome was the number of boxes of respiratory medications prescribed in the 12 months before surgery compared with the 12 months postsurgery. The study defined respiratory medications as oral antihistamines, inhaled bronchodilators, mast cell stabilizers, mucolytic agents, and inhaled corticosteroids.

In the group using respiratory medications before surgery, medication need significantly decreased the year after surgery (RR 0.68; 95% CI, 0.65–0.72). Limitations of this study included unknown percentage of participants carrying a diagnosis of asthma, which may have confounded results in reporting decreased medication use.³

What is the best treatment for cervical radiculopathy from degenerative disorders?

**EVIDENCE-BASED ANSWER**

In chronic cervical radiculopathy, epidural steroid injections, medications with physical therapy, and the combination of both decreases arm and neck pain by 1 to 3 points on an 11-point scale in the first month. Combination therapy is transiently better than the individual treatments for reducing arm pain, but not neck pain (SOR: B, single RCT). In acute cervical radiculopathy, oral prednisone may reduce acute pain and disability compared with placebo over 6 weeks (SOR: C, small RCT). A cervical collar and physical therapy are minimally better in the short term for reducing acute neck and arm pain compared with no intervention, but these differences are likely not clinically relevant (SOR: B, single RCT). Surgery can also be considered for rapid relief (SOR: C, consensus guidelines).

A 2014 multicenter RCT compared the effectiveness of treating chronic cervical radiculopathy in 169 patients with the following modalities: (1) epidural steroid injections up to 3 injections, (2) conservative therapy (nortriptyline and/or gabapentin with physical therapy), or (3) combination therapy (both epidural steroid injections and conservative therapy).¹ Patients had symptoms for an average of 1.3 years and were followed for 6 months. The outcomes were measured by pain reduction rated on a 0 to 10 numerical rating scale.
All 3 groups had significant 1- to 3-point reductions in arm and neck pain compared with baseline. At 1 month, combination therapy resulted in a 1.2-point larger decrease in mean arm pain scores than conservative therapy alone ($<.027$) and a 1.1-point larger decrease than epidural steroid injections alone ($<.045$). No significant differences were noted among the 3 treatment groups for reduction in arm pain at 3 and 6 months or for reduction in neck pain at any time. A key weakness of the study was the lack of a sham injection placebo.¹

A 2013 RCT of 59 patients with proven acute cervical radicular pain by EMG or MRI compared 50 mg prednisone for 5 days with a 5-day taper to placebo for relief of pain over a 6-week period.² Patients had a mean age of 46 years and moderate disability, determined by a neck disability index (NDI) score >15, from neck/shoulder pain for less than 1 month. Pain outcomes were measured on a numerical pain rating scale (NPRS) (0=no pain and 10=maximum pain) and the NDI (0=no disability and 50=greatest perceived disability). All patients also received acetaminophen 325 mg daily.

Disability reduction was greater in the prednisone group than placebo using the NDI score (mean reduction 35.7 vs 12.9; $<.001$) and pain reduction was greater by the NPRS (mean reduction 4.4 vs 1.6; $<.001$). A minimal clinical change in disability (defined as a reduction in NDI score >8.5) occurred in 76% of the prednisone group (22/29) and 30% of the placebo group (9/30) ($<.001$, number needed to treat=2).²

A 2009 RCT of 205 patients compared 3 treatments for acute cervical radiculopathy for 6 weeks: (1) semirigid cervical collar worn for 3 weeks, (2) physiotherapy twice a week for 6 weeks followed by a home program, and (3) no intervention.³ Patients were 18 to 75 years of age and clinically diagnosed with cervical radiculopathy for less than 1 month by a neurologist. All patients received acetaminophen ± NSAID and opiates and were followed for 6 months. Outcomes were based on reduction in neck and arm pain with a 0 to 100 visual analog scale (VAS) and reduction in the NDI (0=no disability to 100=severe disability).

Compared with the no intervention group, both the collar and physiotherapy groups had slightly greater and statistically different weekly reductions in both arm and neck VAS pain scores during the first 6 weeks (see TABLE). Only the collar group had a statistically larger weekly reduction in the NDI score compared with no intervention during the first 6 weeks. All groups had improved pain at 6 months and were not statistically different from each other. This study was not blinded and also lacked well-developed placebo interventions.³

In 2010, the North American Spine Society performed a comprehensive literature review of 317 studies to develop recommendations for the treatment of cervical radiculopathy from degenerative disorders.⁴ Surgical intervention was recommended for rapid relief of symptoms, with a grade of evidence B (fair evidence from a mixture of low-quality RCT, case control, or comparative studies). Surgery was also given as an option for the treatment of single-level degenerative radiculopathy to produce and maintain favorable long-term outcomes (>4 years), with a grade of evidence C (poor-quality evidence from case series or expert opinion). Transforaminal epidural steroid injections using fluoroscopic or CT guidance was recommended, with a grade of evidence C. Cervical traction, oral medications, and physical therapy were also mentioned as options (work group consensus

### TABLE

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>No intervention</th>
<th>Cervical collar</th>
<th>Physiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm pain (0–100 VAS)</td>
<td>−3.1$^a$</td>
<td>−1.9$^b$</td>
<td>−1.9$^a$</td>
</tr>
<tr>
<td>Neck pain (0–100 VAS)</td>
<td>−0.9</td>
<td>−2.8$^b$</td>
<td>−2.4$^a$</td>
</tr>
</tbody>
</table>
| Neck disability index (0–100 scale) | −1.4$^a$ | −0.9$^b$ | −0.8 $^a$Statistically significant reduction from baseline ($<.001$).
$b$Statistically significant difference vs no intervention ($<.05$).

VAS=visual analog scale.

$^a$Statistically significant reduction from baseline ($<.001$).
$b$Statistically significant difference vs no intervention ($<.05$).

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In adults with chronic low back pain, does the use of inhaled cannabis reduce overall opioid use?

**EVIDENCE-BASED ANSWER**

No RCTs have evaluated the potential opioid-sparing effects of inhaled cannabis in patients with chronic low back pain. Smoked cannabis does appear to reduce chronic noncancer pain and neuropathic pain compared with placebo (SOR: B, systematic review of small RCTs). However, patients using cannabis for pain relief are more likely to meet criteria for substance abuse disorders and to be nonadherent with their prescribed opioids (SOR: B, 1 cohort study).

A 2010 systematic review with a 2015 interim update of 29 RCTs (N=1,951) evaluated the efficacy of inhaled and oral cannabis in the treatment of chronic noncancer pain. Six trials evaluated smoked or vaporized cannabis versus placebo for neuropathic pain or pain associated with multiple sclerosis (n=137), and all 6 found small to moderate pain reduction from cannabis compared with placebo (see TABLE). All studies were of short duration with small sample sizes.

A 2014 cohort study evaluated 1,514 adults aged 18 years and older, using prescription opioids for chronic noncancer pain for at least 6 weeks. Data on cannabis use, cannabis use disorder, and cannabis use for pain were collected via phone interviews. The most common pain diagnoses among cannabis users were back or neck problems (84%), arthritis or rheumatism (57%), frequent/severe headaches (50%), and visceral pain (35%).

Persons who used cannabis for pain used a median oral morphine equivalent dose of 100 mg/d (range 60–191) compared with 69 mg/d (range 36–135) in those who did not use cannabis for pain. Among those using cannabis for pain relief (n=237), the average pain relief was 70% with cannabis versus 50% with their other medications (100% meant complete pain relief) (no statistical significance reported).  

Persons using cannabis for pain were more likely to meet criteria for substance abuse disorders (alcohol abuse disorder odds ratio [OR] 3.5; 95% CI, 2.6–4.7; amphetamine use disorder OR 6.3; 95% CI, 4.0–10; illicit opioid use disorder OR 4.3; 95% CI, 2.5–7.6). They were also more likely to be nonadherent with their prescribed opioids during the previous 3 months (34% vs 53%; OR 2.2; 95% CI, 1.6–2.9).

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**GLOSSARY**

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

<table>
<thead>
<tr>
<th>N</th>
<th>Type of pain</th>
<th>Intervention vs comparison</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>HIV sensorineural</td>
<td>Smoked cannabis (3.6% THC) vs placebo cigarettes; 5-day inpatient, 7-day outpatient treatment</td>
<td>&gt;30% pain relief on 100-point VAS</td>
<td>52% with THC vs 24% with placebo; risk difference 28% (95% CI, 2–54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median pain reduction</td>
<td>34% (IQR 16–71) with THC vs 17% (IQR 8–29) with placebo (P=.03)</td>
</tr>
<tr>
<td>38</td>
<td>Neuropathic</td>
<td>Smoked cannabis (3.5% or 7%) vs placebo; 6-hour sessions</td>
<td>Reduction in VAS pain intensity per minute</td>
<td>MD = –0.0035 cannabis vs placebo (95% CI = –0.0063 to –0.0007)</td>
</tr>
<tr>
<td>28</td>
<td>HIV neuropathy</td>
<td>Smoked cannabis (1%–8%) vs placebo; 5-day treatment periods</td>
<td>Change in self-reported pain on 10-point DDS</td>
<td>Median difference 3.3 (P=.016)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;30% pain relief on 100-point VAS</td>
<td>46% (95% CI, 28–65) with cannabis vs 18% (95% CI, 3–32) with placebo (P=.043)</td>
</tr>
<tr>
<td>21</td>
<td>Neuropathic</td>
<td>Smoked THC (9.4% vs 0%); 14-day treatment periods</td>
<td>Mean daily pain intensity on 11-point NRS</td>
<td>5.4 with 9.4% THC vs 6.1 with 0% THC; MD 0.7 (95% CI, 0.02–1.4)</td>
</tr>
<tr>
<td>30</td>
<td>Multiple sclerosis</td>
<td>Smoked cannabis (4% THC) vs placebo; daily for 3 days</td>
<td>Mean change in pain from baseline on 100-point VAS</td>
<td>8.3 (95% CI 4.5–14) with THC vs 3.0 (95% CI 0.04–6.6) with placebo (P=.008)</td>
</tr>
<tr>
<td>39</td>
<td>Neuropathic</td>
<td>Vaporized cannabis (3.5% &amp; 1.3% THC) vs placebo; three 6-hr sessions</td>
<td>&gt;30% pain relief on 100-point VAS</td>
<td>61% (95% CI, 45–75) with 3.5% THC, 57% (95% CI, 41–71) with 1.3% THC, 26% (95% CI, 15–42) with placebo (P&lt;.01 for both cannabis doses vs placebo; P&gt;.7 between cannabis doses)</td>
</tr>
</tbody>
</table>

DDS = descriptor differential scale; IQR = interquartile range; MD = mean difference; NNT = number needed to treat; NRS = numeric rating scale; THC = tetrahydrocannabinol; VAS = visual analog scale.