What nonpharmacologic therapies for patients with chronic vertigo, not from Meniere’s disease, are effective for the relief of symptoms?

Evidence-based answer
For benign paroxysmal positional vertigo (BPPV), the Epley maneuver is effective; adding post-Epley activity restrictions does not result in further improvement (SOR: A, meta-analyses). For unilateral peripheral vestibular dysfunction from multiple etiologies, vestibular rehabilitation exercises are helpful (SOR: A, meta-analysis and RCT).

Evidence summary
Epley maneuver
A 2004 Cochrane review of 5 RCTs (N=292) evaluated the Epley maneuver for treatment of BPPV in adults diagnosed by a positive Dix-Hallpike test. The Epley canalith repositioning maneuver was performed “as classically described” and compared with no treatment in 1 trial and sham maneuver in 4 trials. Outcomes were assessed immediately in 1 study and the longest duration of follow-up was 4 weeks.

Compared with no treatment or sham treatment, the Epley maneuver resulted in significantly more patients achieving complete resolution of symptoms (56% vs 21%; OR 4.4; 95% CI, 2.6–7.4). The studies were generally rated as low risk of bias and although patients were not blinded, the outcome assessors were.¹

A 2012 Cochrane review of 11 RCTs (N=855) evaluated the efficacy of modifications to the Epley maneuver in adults with posterior canal BPPV diagnosed by a positive Dix-Hallpike test.² Nine studies (n=528) evaluated post-Epley postural restrictions such as wearing a neck brace, restricting head movements, or modifying sleep position.

Compared with the Epley maneuver alone, the addition of post-Epley postural restrictions did not significantly increase the number of patients with complete resolution of symptoms, but did significantly increase the conversion to a negative Dix-Hallpike test.
In Depth

Evidence-Based Practice / March 2015

(RR 1.1; 95% CI, 1.1–1.2). Vibration to the mastoid region and adding more steps to the Epley maneuver were not effective.

Vestibular rehabilitation exercises

A 2011 Cochrane review of 27 RCTs (N=1,668) evaluated vestibular rehabilitation exercises or movement-based programs in adults with vestibular dysfunction of unilateral peripheral origin from multiple etiologies (including some patients with Meniere’s disease). In 4 studies (n=565), 49% of patients receiving vestibular rehabilitation reported improvement in dizziness compared with 26% of patients receiving sham, routine care, or no treatment (OR 2.7; 95% CI, 1.9–3.9). These 4 studies were rated as low risk of bias, but 2 of the studies did not blind outcome assessors.

An RCT (N=337) evaluated the effect of home vestibular rehabilitation exercises compared with routine medical care on dizziness resolution in adults with chronic vestibular dizziness recruited from general practices in England. Patients were divided into 3 groups. The booklet plus phone support group received a validated booklet providing instructions on vestibular rehabilitation exercises to be performed twice a day for 3 months with telephone support on 3 occasions. The second group received the booklet only (without telephone support) and the third group received routine care.

At 3 months, 57% of patients receiving the booklet plus phone support and 59% of patients receiving the booklet only reported improved symptoms compared with 37% of patients receiving routine care (OR 2.3; 95% CI, 1.3–3.9; and 2.4; 95% CI, 1.4–4.2). At 12 months the difference between the booklet only group and routine care group was no longer significant, but the booklet plus phone support group remained significantly better, with 69% reporting improved symptoms compared with 47% of the routine care group (OR 2.6; 95% CI, 1.4–4.7). The improved symptoms persisted at 12 months even though only 44% in booklet plus phone support group and 34% in the booklet only group fully adhered to the 3-month exercise program.

Razieh Hadian Jazi, MD
Thomas Satre, MD
University of Minnesota
St. Cloud, MN

REFERENCES

LETTERS TO THE EDITOR

COUNT FOR SCHOLARLY ACTIVITY!

The ACGME classifies Letters to the Editor as scholarship of integration. *Evidence-Based Practice* wants your “op-eds explaining the meaning and significance of a current public health concern” or “analysis of the results of a paper published by others.”

Share your knowledge and submit your letter to the editor of *Evidence-Based Practice* via www.fpin.org/letters.

Predicting the MRI results

I am very proud of my clinical knee exam and consider myself something of an expert at finding meniscal tears—the most common internal derangement of the knee in my patient panel. Using the Apley compression test and draw signs, more than 90% of the patients I send to MRI for confirmation of a meniscal tear actually have one. I love telling patients that my exam was confirmed by the MRI! Usually, then, my patients are referred to an orthopedic surgeon for meniscal resection.

At least, that is how things have gone for a long time. But I and the medical community at large have apparently been placing our trust in a pain-management strategy (meniscectomy) that had never been rigorously tested—until now.

In an article published in the New England Journal of Medicine, researchers decided to create a study of meniscal surgery using a sham surgical control.1 Researchers randomized 146 patients with a nontraumatic meniscal tear (and little or no arthritis of the knee) to either meniscal repair or fake meniscal repair. Every patient started with an arthroscopy and, once the internal damage was confirmed, received either meniscectomy or some detailed stagecraft during which the surgeons made noise and pantomimed a surgical procedure. Then everyone received the same graded exercise program.

One year later, no difference was noted between the 2 groups—not in pain, function, repeat procedures, or complications. This finding suggests that one of the most common orthopedic procedures in the United States may not do a dang thing over the long term. The study authors, citing prior corroborating research, ventured that meniscal tears may be an early indicator of arthritis of the knee and not a separate clinical problem requiring intervention.

But if surgery is not indicated, then the MRI is not indicated either. And if the MRI is not indicated, then I will no longer be able to show off my clinical prowess for diagnosing meniscal tears in quite the same, highly visible way. Dang it!

I can only hope that the “street cred” I have just lost as a diagnostician will be fully regained by steering my patients away from a needless procedure.

Jon O. Neher, MD

REFERENCE

Diving for PURLs

Don’t delay: Start statins before you stent

This meta-analysis of 20 RCTs representing a total of 8,750 patients with acute coronary syndrome was designed to determine whether initiating statins before or after percutaneous coronary intervention (PCI) made a difference in the primary outcomes of mortality and myocardial infarction (MI).

Secondary outcomes included other major adverse cardiac events (MACEs), comprising the 30-day composite of MI, cardiovascular death, and target revascularization, and major adverse cerebrovascular events (MACCEs, defined as the composite of death, nonfatal MI, and nonfatal stroke).

Statins given prior to PCI resulted in a 62% reduction of MI in patients with ACS at 30-day follow-up compared with no statin or low-dose statin (OR 0.38; 95% CI, 0.24–0.59; P<.0001), but not statins administered after PCI. Although the trends for benefit of starting a statin prior to PCI continued long term, the difference did not reach statistical significance for MI (OR 0.81; 95% CI, 0.65–1.01; P=.06) while there was a significant reduction in MACE (OR 0.52; 95% CI, 0.37–0.73; P=.0002). The 30-day incidence of MACE was 5.29% (166 of 3,139) in the statin group and 8.17% (253 of 3,096) in the control group.

<table>
<thead>
<tr>
<th>Relevant</th>
<th>Yes</th>
<th>Medical care setting</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td>Yes</td>
<td>Implementable</td>
<td>Yes</td>
</tr>
<tr>
<td>Change in practice</td>
<td>Yes</td>
<td>Clinically meaningful</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Bottom line: In patients with acute coronary syndromes, initiating statin therapy before PCI, ie, angioplasty, is strongly associated with a reduction in recurrent MI and death.

Review and Summary Author: Sonia Oyola, MD, The University of Chicago, Chicago, IL

Statin plus standard care for venous ulcers

This randomized double-blind study compared the effectiveness and safety of simvastatin versus placebo for venous ulcers. Sixty-six patients from a dermatology outpatient department between the ages of 41 and 71 years with ≥1 ulcers less than 10 cm and who had open ulcers for at least 3 months were included.

Patients were separated in groups according to ulcer size (≤5 cm and >5 cm). All patients received standard care (wound cleansing with saline solution, saline compresses twice daily, compression therapy, and leg elevation) plus 1 tab daily of simvastatin 40 mg or placebo. At baseline, ulcer diameter and surface area were measured. Patients were seen by the same dermatologist every 2 weeks and photos were taken until wound closure or up to 10 weeks.

The primary outcome was the proportion of patients with complete healing in both groups. Secondary outcomes included time to complete healing and percentage of surface area healed.

Among patients in simvastatin group, 90% had complete ulcer closure compared with 34% of patients in control group (RR 2.6; 95% CI, 1.59–4.28). All patients received standard care (wound cleansing with saline solution, saline compresses twice daily, compression therapy, and leg elevation) plus 1 tab daily of simvastatin 40 mg or placebo. At baseline, ulcer diameter and surface area were measured. Patients were seen by the same dermatologist every 2 weeks and photos were taken until wound closure or up to 10 weeks.

<table>
<thead>
<tr>
<th>Relevant</th>
<th>Yes</th>
<th>Medical care setting</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td>Yes</td>
<td>Implementable</td>
<td>Yes</td>
</tr>
<tr>
<td>Change in practice</td>
<td>Yes</td>
<td>Clinically meaningful</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Bottom line: This small study supports the use of simvastatin in combination with standard wound care and compression for the treatment of venous ulcers.

Review and Summary Author: Kortnee Roberson, MD, The University of Chicago, Chicago, IL

Additional information regarding the PURLs and Diving for PURLs series can be found at: http://www.fpin.org/purls-faqs/
Diving for PURLs

Evidence-Based Practice / Vol. 18, No. 3

Increased duration of labor with epidurals

This retrospective cohort study of 42,268 women who delivered cephalic singletons vaginally during the years of 1976–2008 compared the duration of the second stage of labor in women with and without epidurals. Women with the following risk factors were excluded: placenta previa, intrauterine fetal demise, or known lethal congenital anomalies.

The primary outcomes evaluated were the median and 95th percentile times for length of second stage of labor.

Epidurals prolonged the second stage in both nulliparous (120 vs 47 min; P<.001) and multiparous women (38 vs 14 min; P<.001). The rate of birth trauma increased in the prolonged second stage group (OR 1.58; 95% CI, 1.13–2.22) while other secondary outcomes were similar.

<table>
<thead>
<tr>
<th>Relevant</th>
<th>Yes</th>
<th>Medical care setting</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td>No</td>
<td>Implementable</td>
<td>Yes</td>
</tr>
<tr>
<td>Change in practice</td>
<td>No</td>
<td>Clinically meaningful</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Bottom line:** Epidurals prolong the second stage of labor. Prolonged second stage appears to lead to higher rates of birth trauma. However, management of the second stage of labor has changed substantially since 1976–2008 and this study did not address if passive descent had been used during this time period. It may be useful to remind patients that epidurals will prolong labor, but no conclusion can be made about the effects of this prolongation to reliably guide practice.

**Review and Summary Authors:** Ami Goldstein, MSN, CNM, FNP, and Anne Mounsey, MD, University of North Carolina at Chapel Hill, Chapel Hill, NC

Aspirin for all?

This systematic review determined the overall benefits and harms of prophylactic aspirin use in the general population. The authors identified randomized controlled trials and observational studies estimating the effect of prophylactic aspirin in varying doses on the incidence of cancer, cardiovascular disease, major extracranial bleeding, and mortality. They completed a benefit-harm analysis, estimating the effect of aspirin use (starting at ages 50, 55, 60, and 65) on mortality and major events, defined as cancer, myocardial infarction, stroke, or major extracranial bleeding.

Over 10 years aspirin decreased the major event rate 0.79% to 2.03% (absolute), with the largest net benefit occurring in older men. The number of individuals needed to treat with aspirin for 10 years to prevent one major event was 33–127. The net benefit of 20 years of aspirin use in terms of reduction in mortality was estimated to range from 0.47% to 2.18% fewer deaths. The number needed to treat with aspirin for 20 years to prevent one death was 46–213.

<table>
<thead>
<tr>
<th>Relevant</th>
<th>Yes</th>
<th>Medical care setting</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td>Yes</td>
<td>Implementable</td>
<td>Yes</td>
</tr>
<tr>
<td>Change in practice</td>
<td>No</td>
<td>Clinically meaningful</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Bottom line:** This study reinforces current US Preventive Services Task Force guidelines recommending prophylactic aspirin use in older adults. It is unclear from these data whether higher dose aspirin should be recommended, or whether the benefits of prophylactic aspirin continue to outweigh the harms in individuals aged 70 years and older.

**Review and Summary Author:** Kate Kirley, MD, MS, The University of Chicago, Chicago, IL

Diving for PURLs Team

The University of Chicago, Department of Family Medicine
Goutham Rao, MD, Diving for PURLs Editor-in-Chief
Mari Egan, MHPE, MD Katheerine Kirley, MD Debra Stulberg, MD
Kohar Jones, MD Sonia Oyola, MD Kortnee Roberson, MD
Dionna Brown, MD Jennifer Bello, MD Liz Nguyen, MD
Rush–Copley Medical Center, Department of Family Medicine
Kate Rowland, MD, PURLs Editor-in-Chief & Diving for PURLs Deputy Editor
Northshore University Health System, Department of Family Medicine
Janice Benson, MD Pooja Saigal, MD

University of Missouri, Department of Family Medicine
Jim Stevermer, MD, MSPH, PURLs Deputy Editor
Erik Lindbloom, MD, MSPH

University of North Carolina, Department of Family Medicine
Anne Mounsey, MD, PURLs Deputy Editor

University of Minnesota, Department of Family Medicine
Shailendra Prasad, MD, MPH
University of Pittsburgh Medical Center, St. Margaret Family Medicine
Nil Das, MD
EBM on the Wards

BID vs TID dosing of unfractionated heparin for venous thromboembolism (VTE) prophylaxis in hospitalized patients

Case
A 64-year old man with a history of COPD presents with worsening shortness of breath, 5 days of cough, increased sputum production, malaise, and fever. Vitals are significant for tachypnea (rate 28 bpm), and hypoxia (82% on room air). His BMI is 41. Physical exam reveals no JVD or lower extremity edema, but prominent expiratory wheezes bilaterally. Chest radiography reveals hyperinflated lungs. Writing your admission orders for a COPD flare, you wonder if the patient should receive BID or TID dosing of subcutaneous unfractionated heparin for VTE prophylaxis.

Review of the evidence
A 2011 meta-analysis of 16 RCTs involved nearly 28,000 hospitalized nonsurgical, nonstroke patients with conditions including heart failure, respiratory disease, and infection. It examined the effectiveness of BID versus TID dosing of 5,000 units of subcutaneous unfractionated heparin (UFH) for deep vein thrombosis (DVT) prophylaxis. The authors used a mixed-treatment analysis, which included indirect comparisons from RCTs that had 1 randomization arm in common (allowing comparisons of UFH doses from trials that used UFH and other comparators).

No statistically significant difference was noted between UFH BID and TID dosing in the rate of pulmonary embolism (PE) (16 trials, N=27,667; risk ratio [RR] 1.7; 95% CI, 0.49–208), DVT (13 trials, N=9,822; RR 1.5; 95% CI, 0.64–4.3), major bleeding (defined individually by each trial) (14 trials, N=25,122; RR 0.89; 95% CI, 0.08–7.1), or death (12 trials, N=27,135; RR 1.2; 95% CI, 0.72–2.0) within a follow-up period of 6–90 days. The study authors stated the wide confidence intervals were due to the small number of events and concluded there was no difference in UFH dosing on major endpoints based on moderate-quality evidence. This analysis did not examine dosing effectiveness in overweight or obese populations.

The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on the prevention of VTE recommend following the manufacturer-suggested dosing for individual antithrombotic agents (Grade 1C–, “strong recommendation/low quality of evidence”) and that dosing for UFH should be every 8–12 hours. The guidelines also recommend every general hospital have a policy that addresses a strategy to prevent VTE in the hospitalized patient (Grade 1A–, “strong recommendation/high quality of evidence”).

Case Wrap-Up
Either BID or TID dosing of UFH are appropriate choices for this patient. There does not appear to be a difference in DVT, PE, major bleeding, or mortality based on the schedule of heparin dosing, although studies in obese populations are lacking.

Melissa Noble, MD
Corey Lyon, DO
University of Colorado FMR
Denver, CO

REFERENCES
Should we screen for osteoporosis using calcaneal ultrasound?

Evidence-Based Answer

Calcaneal ultrasound should not be used to screen for osteoporosis because of the wide variation in sensitivity and specificity. Further research is needed to determine the correlation between dual energy X-ray absorptiometry (DEXA) scan and calcaneal ultrasound for osteoporosis screening or diagnosis (SOR: B, systematic review of cohort trials).

A 2011 systematic review including 6 cohort trials evaluated quantitative calcaneal ultrasound (QUS) for diagnosing individuals with osteoporosis, using DEXA scan of the femoral head and lumbar spine as the gold standard. The review included 12,250 men and women 20–85 years old, who were not taking medications that altered bone density and did not have comorbidities that could alter bone quality.

These studies found sensitivities ranging from 49% to 95% and specificities ranging from 30% to 90% when compared with the gold standard. The authors concluded that QUS cannot be used to diagnose osteoporosis because of the high variability of the sensitivities and specificities.

A 2011 prospective cohort study of 43 women aged 62–87 years evaluated DEXA, QUS, and quantitative computed tomography for the diagnosis of osteoporosis. Osteoporosis was defined as a T-score of −2.5 or less, based on femoral neck DEXA as the gold standard.

Compared with the gold standard, QUS showed a sensitivity of 100% and a specificity of 66% for diagnosing osteoporosis (negative likelihood ratio of 0; positive likelihood ratio of 2.9). The authors concluded that QUS can accurately rule out osteoporosis, but may produce a higher false-positive rate than femoral neck DEXA and lacks generally accepted T-score thresholds for the diagnosis of osteoporosis.

Jenna Silakoski, DO
Aaron Williams, DO
Carl R. Darnall Army Medical Center FMR
Fort Hood, Texas

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 US Army at large, or the Department of Defense.


Does cranberry juice or cranberry extract reduce the frequency of recurrent urinary tract infections in women?

Evidence-Based Answer

In general, cranberry products do not appear to prevent recurrent urinary tract infections (UTIs) in women (SOR: B, Cochrane review and consistent RCTs with methodological flaws). However, there may be a small benefit for women older than 50 years (SOR: C, subgroup analysis in small RCT).

A 2012 Cochrane systematic review of 8 RCTs (N=1,223) evaluated the effectiveness of varying doses of cranberry juice (240–600 mL daily) as well as cranberry capsules (400, 500, and 1,000 mg/d) against several comparators for the prevention of UTIs. Studies included adult, nonpregnant women 18–80 years old with a history of at least 2 symptomatic UTIs in the previous year.

With follow-up at 3 to 12 months, cranberry therapy had no greater effect on recurrent UTI incidence than placebo (4 trials, N=594; 19% vs 30%; risk ratio [RR] 0.74; 95% CI, 0.42–1.3). Also, no difference was noted in recurrent UTIs in the cranberry group compared with the antibiotic prophylaxis group at 12 months (2 trials, N=344; 51% vs 40%; RR 1.3; 95% CI, 0.85–2.0). One RCT (N=99) showed cranberry products were more effective at preventing UTIs than probiotics (RR 0.41; 95% CI, 0.20–0.85). There was no difference in adverse gastrointestinal effects (2 trials, N=344; RR 0.78; 95% CI, 0.42–1.4) or skin reactions (1 trial, N=207; RR 0.54; 95% CI, 0.25–1.2) between women taking cranberry products compared with antibiotics. There also was no difference in effectiveness between twice-daily and once-daily dosing (2 trials, N=83; RR 1.1; 95% CI, 0.75–1.7). The Cochrane review concluded cranberry products do not appear to have a significant benefit in preventing UTIs.

Potential weaknesses of the studies included small sample size in most studies as well as attrition bias related to high dropout rates. Many studies did not explicitly state the concentration of active ingredients. Also, many participants in the studies were not included in the statistical analysis.

A subsequent RCT of 213 adult Japanese women with a mean age 57 and more than 1 UTI during the preceding year compared the effectiveness of
125 mL (containing >40 mg proanthocyanidins, an active ingredient) of daily cranberry juice versus placebo beverage for preventing recurrent UTI at 24 months’ follow-up.\(^2\)

Overall, no statistically significant difference was noted between the cranberry and placebo groups (30% vs 36%; \(P=.42\)). Subanalysis by age showed that cranberry use in women older than 50 years reduced the incidence of recurrent UTI (29% vs 49%; \(P=.045\)), an effect not seen in women younger than 50 years. An adverse event of throat discomfort was reported in 1 participant in the treatment group. Limitations of the study included a small number of younger, premenopausal women with low UTI recurrence rates.\(^2\)

A 2012 double-blind RCT of 176 adult women aged 18–45 with a history of 1 or more clinician-diagnosed UTIs in the past 12 months at 2 centers examined the effectiveness of cranberry juice compared with placebo for preventing UTI.\(^3\) At 6 months, the Kaplan-Meier curve showed no statistically significant difference in time to first symptomatic UTI (\(P=.41\)) or number of patients with UTI episode (29% vs 37%; adjusted HR 0.68; 95% CI, 0.33–1.4).

No significant adverse effects were reported in the study, and reported adherence to the intervention was high. The study was underpowered to find a small difference. An additional limitation was the inability to measure adherence to interventions other than per report.\(^3\)

**Evidence-Based Answer**

Soy formula feeding has no effect on growth (SOR: A, systematic review of RCTs and cohort studies with consistent results). Soy formula has been associated with extremely premature thelarche (prior to age 2) and increased duration and discomfort of menses in adulthood (SOR: C, case-control and cohort studies with multiple comparisons). But the American Academy of Pediatrics states that there is no convincing evidence that soy formulas affect human development, reproduction, or endocrine function (SOR: C, expert opinion).

A 2011 systematic review of 26 RCTs, cohort studies, and case-control studies (N=22,013) commissioned by the National Toxicology Program’s Center for the Evaluation of Risks to Human Reproduction evaluated the developmental effects of feeding soy formula to infants.\(^1\) Ten mostly small RCTs and cohort studies (N=2,146) compared infants fed soy formula, breast milk, and cow-milk formula in relation to various growth parameters such as weight, length, and head circumference. No consistent differences in growth were seen among the infant groups at 1 year of age.

One retrospective case-control study in the review evaluated girls with premature thelarche (N=130) compared with age-matched controls. Thelarche prior to age 2 was associated with soy formula feeding (OR 2.7; 95% CI, 1.1–6.8). Alternatively, when onset of premature thelarche was not restricted to younger than age 2, there was no association between soy formula feeding and premature thelarche.\(^1\)

A retrospective cohort study in the review of 811 adult women fed either soy formula or cow-milk formula as infants evaluated more than 30 outcomes in adults. Compared with women fed cow-milk formula, women fed soy formula as infants reported slightly longer duration of menses (adjusted mean difference, 0.37 days; 95% CI, 0.06–0.68 days), with no change in severity of menstrual flow. Women fed soy formula as infants also reported greater menstrual discomfort (unadjusted relative risk for extreme discomfort vs no or mild pain, 1.7; 95% CI, 1.0–3.0). After adjustment for multiple comparisons of the numerous endpoints, the authors reported these findings were no longer significant.\(^1\)
Also included in the systematic review, single cohort and case-control studies found no association between soy formula use and adult breast cancer, childhood diabetes mellitus type 1, or childhood cognitive performance. The authors of this systematic review concluded there is minimal concern for adverse effects on growth and development in infants who consume soy infant formula. Common limitations noted were the nonrandom method of assignment to feeding groups, the use of self-selected breast- and formula-feeding mothers, failure to control for the reason soy formula was used, and inconsistent introduction of solid foods.\(^1\)

In 2008, the American Academy of Pediatrics Committee on Nutrition reported that numerous studies have documented normal growth and development in term neonates fed soy-based formula and concluded, “There is no conclusive evidence from animal, adult human, or infant populations that dietary soy isoflavones affect human development, reproduction, or endocrine function.”\(^2\) Level of evidence indicators were not included.

## Is there any benefit to continuing cervical Pap smears for women older than 65 with a history of normal Pap results?

### Evidence-Based Answer

Women older than 65 years who have been screened regularly and have had normal Pap smears do not need to continue Pap screening (SOR: A, evidence-based guideline, RCTs, and case-control trials).

The current US Preventive Services Task Force recommendation for cervical Pap smear screening in women older than 65 is to discontinue screening for women who have had adequate prior screening and are not otherwise at high risk for cervical cancer (Grade D, not recommended).\(^3\) The American Cancer Society (ACS)/American Society for Colposcopy and cervical pathology (ASCCP)/American Society of Clinical Pathology (ASCP) guidelines define adequate prior screening as 3 consecutive negative cytology results or 2 consecutive negative human papillomavirus (HPV) results within 10 years before cessation of screening, with the most recent test occurring within 5 years. A large randomized, population-based case-control study done in the United Kingdom analyzed 1,341 women diagnosed with cervical cancer at age 65–83, with 2,646 age-matched controls examining the outcome of cervical cancer according to Pap screening history.\(^2\) Women with adequate negative screening at age 65 had a lower 20-year risk of cancer than women without screening between the ages of 50 and 64 (8 cancers per 10,000 women vs 49 cancers per 10,000 women, \(P<.01\)). Compared with patients who did not have adequate screening before age 65, patients with adequate screening before age 65 had a lower risk of cervical cancer (OR 0.25; 95% CI, 0.21–0.30). This study was based on Pap cytology screening only, not HPV screening.

A modeling analysis based on evidence synthesis of 3 randomized and 1 natural history study was developed as part of a previous evidence report prepared for the Agency for Healthcare Research and Quality.\(^3\) The model describes the natural history of HPV infection, including progression to CIN2–3 and cancer, as well as the effect of screening and treatment on the prevention of disease progression in a cohort of unvaccinated girls who are followed until either death or age 100 years.

Continued screening of women with regular normal Pap smears to age 90 would prevent only 0.5 deaths per 1,000 screened women, and would extend life expectancy by only 1 year per 1,000 women and result in an additional 127 colposcopies. The authors stated the benefits of screening after age 65 do not outweigh the harms, even for women with new sexual partners.\(^3\)

## References

In adult patients with chronic sinusitis, what are the indications for specialist referral?

Evidence-Based Answer
The answer is unclear. Patients with chronic sinusitis who have failed medical management may benefit from referral for functional endoscopic sinus surgery (FESS). The intervention likely improves symptoms. However, FESS does not appear to improve cure rates (SOR: B, heterogeneous RCTs).

In 2008, a Cochrane review of 3 RCTs (N=212) examined the effectiveness of FESS compared with medical treatment for chronic rhinosinusitis (CRS). The first of these trials found that FESS is similar to medical treatment (sinus irrigation with and without antibiotics) in cure rates at 1 year (N=89; OR 1.6; 95% CI, 0.58–4.5). However, the presence of purulent rhinitis decreased from 91% to 40% after sinus irrigation and from 86% to 16% after sinus irrigation followed by FESS (P=.027). The incidence of loss of smell decreased from 49% to 18% after sinus irrigation and from 51% to 11% after sinus irrigation followed by FESS (P=.026). The second prospective RCT (N=29) compared FESS with inferior meatal antrostomy, and found no difference in symptom score at 6 weeks to 12 months of follow-up (weighted mean difference 1.4; 95% CI, –3.8 to 6.5). One year after surgery, 44% of the antrostomy patients and 89% of the FESS patients reported distinct improvement of their symptoms. The third RCT (N=90) reviewed in the Cochrane evaluated medical and surgical treatment of patients with polypoid and nonpolypoid CRS for 12 months. No statistical difference was noted in percentage change in symptoms between the surgical and medical groups (52% vs 50%; P>.05). A systematic review of 33 trials (3 RCTs, 3 nonrandomized comparative studies, 27 case series reports; N=8,208) evaluated the clinical effectiveness of FESS for nasal polyps. Most studies were not pooled and reported improvement in symptoms after FESS with relatively few complications. The studies could not be compared due to differences in study design.

In 2011, Allergy, Asthma & Clinical Immunology and the Journal of Otolaryngology-Head and Neck Surgery co-published opinion-based guidelines for CRS that stated surgery should be considered in individuals who fail medical treatment (moderate recommendation; based on expert opinion, accept with some reservation).

In addition, patients with stable CRS who develop changes suggesting a complication, such as orbital cellulitis, cavernous vein thrombosis, or erosion into the central nervous system, should be urgently evaluated by a specialist.

Megha Manek, MD  
Chahal Kashif, MD  
Rachna Tiwari, MD  
Guthrie Robert Packer Hospital  
Sayre, PA


Is spinal manipulation therapy more effective than home exercise as a treatment for neck pain?

Evidence-Based Answer
No, spinal manipulation is no more effective than home exercise for relief of acute or subacute neck pain (SOR: B, single RCT). For chronic neck pain in patients older than 65 years, the combination of spinal manipulation and home exercise may be more effective in the short term than home exercise alone, but this difference disappears in the long term (SOR: B, small RCTs). No studies used sham manipulation as a control.

In 2012, an unblinded, but randomized trial compared spinal manipulation, home exercise, and medication for the treatment of acute and subacute neck pain in 272 patients aged 18 to 65 years old. The spinal manipulation group received high-velocity, low-amplitude manipulation of the neck and low-velocity joint mobilization of the neck for 12 weeks conducted by 6 chiropractors, while the home exercise group received instruction in neck and shoulder stretching to be completed 6 to 8 times a day over 12 weeks.

Compared with baseline, the spinal manipulation group improved an average of 3.8 points (95% CI, 3.3–4.2) on a 0- to 10-point pain scale after 12 weeks and 3.6 points (95% CI, 3.1–4.0) after 52 weeks, while the home exercise group improved 3.3 points (95% CI, 2.9–3.7) at 12 weeks and 3.1 points (95% CI, 2.5–3.7) at 52 weeks. The differences between groups were not statistically significant.
A 2014 unblinded, but randomized trial compared spinal manipulation plus home exercise with home exercise alone in 241 adults older than 65 years with chronic neck pain of at least 12 weeks’ duration. A third group received supervised exercise plus home exercise. The 79 patients randomized to home exercise alone received instruction on stretching and strengthening exercises for the neck and upper body to be done daily over 12 weeks. The 80 patients randomized to spinal manipulation plus home exercise received the same home exercises plus spinal manipulation to the neck modified by 1 of 11 chiropractors to accommodate each patient that included thrust techniques and low-velocity mobilization over 12 weeks.

The addition of spinal manipulation to home exercise led to mean pain ratings of 1 point less on a 0-to-10-point scale compared with home exercise alone at 12 weeks (mean difference [MD] –1.0; 95% CI, –1.6 to –0.5). However, this difference became nonsignificant at 26 and 52 weeks.

A 2010 unblinded, randomized pilot study compared spinal manipulation plus home exercise with home exercise alone in 20 adults with chronic neck pain for at least 3 months recruited through advertisements. The spinal manipulation plus home exercise group received 4 weeks of high-velocity, low-amplitude spinal manipulation of the neck followed by instruction in isometric, dynamic, and aerobic exercises to be completed 3 times per week for 8 weeks. The home exercise group had a 4-week waiting period before completing the same exercise program.

At 12 weeks, pain, as measured on a 0–100 visual analog scale, decreased significantly from baseline for both spinal manipulation plus home exercise (from 34 to 17; P<.005) and home exercise alone (from 33 to 20; P<.005), but no significant differences were noted between the groups. Being a pilot study, there was not enough power to detect between-group differences. The investigators determined a sample size of 176 would be needed for this outcome.

Evidence-Based Answer
Currently evidence suggests that coenzyme Q10 (CoQ10) is probably not effective for statin-related myalgia (SOR: C, heterogeneous RCTs).

Does coenzyme Q10 supplementation help reduce statin-induced myalgia?

An RCT of 76 patients (42% male, mean age 62 years) assessed the effect of CoQ10 60 mg twice daily or placebo on statin-induced myalgia (SIM; defined as new onset of symptoms in ≥2 extremities within 60 days of starting stain therapy). Statin therapy included simvastatin (n=44), pravastatin (n=15), atorvastatin (n=14), and rosuvastatin (n=3). SIM pain was evaluated monthly with a 10-cm visual analog pain scale (VAS).

Five patients in the CoQ10 group and 3 in the placebo group discontinued the study because of myalgias. Mean VAS score at baseline was 6 cm for both groups. At 1 month, no significant difference for VAS score was observed between the CoQ10 and placebo groups (3.9 cm vs 4 cm; P=.97).

An RCT assessing the benefit of CoQ10 and selenium supplementation for SIM randomized 60 myopathic patients (32% male, mean age 58 years) to 1 of 4 groups: 200 mg/d CoQ10 plus 200 mcg/d selenium; 200 mg/d CoQ10 plus selenium placebo; CoQ10 placebo plus 200 mcg/d selenium; or double placebo over 12 weeks. Statin therapy included simvastatin (n=14), fluvastatin (n=5), atorvastatin (n=25), and rosuvastatin (n=16). SIM symptoms were assessed monthly using a VAS (0–10 scale) for each symptom of muscle pain, muscle weakness, muscle cramps, and fatigue.

Selenium supplementation produced no improvement for myalgia, so results were reported for CoQ10 supplementation only. Compared with placebo, after 12 weeks of treatment with CoQ10, decrease in muscle pain was significantly greater (–3.5 vs –0.1; P<.01) and improvement of muscle weakness was significantly greater (–4.2 vs –0.84; P<.01). Compared with placebo, CoQ10 supplementation also significantly improved muscle cramping (–3.5 vs –0.43; P<.01) and statin-associated fatigue (–5.5 vs –2; P<.01).

A prospective, double-blinded RCT assessed possible benefit of CoQ10 and selenium on SIM for 43 patients who had experienced myalgia on...
atorvastatin therapy. After a 6-week washout period off statin therapy, patients resumed a regimen with 10 mg atorvastatin daily. Those developing SIM (n=41) continued atorvastatin therapy and were randomized to either 400 mg CoQ10 and 200 mcg selenium daily or matching double-placebo. SIM was assessed using 3 validated measures: a pain VAS, the Giessener Check List, and the Buss-Perry Aggression Questionnaire.

After 12 weeks of therapy, no statistically significant differences in SIM scores was noted between the CoQ10 plus selenium or placebo groups.

A 2012 multivariate analysis using prospective cohort data from the Matlab demographic surveillance system in Bangladesh assessed 10,435 pregnancies that ended in miscarriage and were followed by another pregnancy. After adjustment for maternal age, gravidity, education level, area of domicile, and calendar year, confirmed pregnancies less than 3 months after a miscarriage were less likely to result in a second miscarriage (adjusted risk ratio [aRR] 0.70; 95% CI, 0.57–0.86) compared with IPIs of 6 to 12 months. A prospective cohort study assessed 4,619 Egyptian women who experienced a first trimester miscarriage in their first pregnancy and subsequently became pregnant. Women were excluded if the first pregnancy gestational age was <5 weeks or >14 weeks, if calculated IPI was <4 weeks, or if they had nonsingleton pregnancies.

After adjustment for maternal age at first pregnancy, women who conceived within 6 months of a miscarriage (n=2,422) had a lower rate of stillbirth (aOR 0.45; 95% CI, 0.21–0.56) and were less likely to experience a threatened abortion (aOR 0.30; 95% CI, 0.19–0.38) or ectopic pregnancy (aOR 0.77; 95% CI, 0.62–0.91) compared with the group who conceived after 12 months (n=2,197). With regard to spontaneous abortion, no significant difference was noted (aOR 0.42; 95% CI, 0.26–1.0). Women who conceived within 6 months of an initial miscarriage were also less likely to have preterm delivery (aOR 0.83; 95% CI, 0.67–1.0) or an infant weighing <2,500 g (aOR 0.83; 95% CI, 0.71–0.91) compared with an IPI of longer than 12 months.

How long should a patient wait before attempting pregnancy again after a spontaneous abortion?

Evidence-Based Answer

Women who conceive 1–6 months after pregnancy loss have a lower rate of subsequent miscarriage, ectopic pregnancy, preterm birth, neonatal death, or still birth in the subsequent pregnancy than women conceiving after 6 months (SOR: B, large prospective and retrospective cohort studies). However, no trials specifically address when women should attempt to conceive after a spontaneous abortion.

A 2010 population-based, retrospective cohort study included 30,937 Scottish women who miscarried during their primary pregnancy and subsequently became pregnant. Data were adjusted for maternal age at first pregnancy event, socioeconomic status, and year of first pregnancy. Women who had nonsingleton pregnancies or with an inter-pregnancy interval (IPI) less than 4 weeks were excluded.

Compared to those with IPIs of 6 to 12 months, women with an IPI of less than 6 months were found to have a decreased risk of miscarriage (adjusted odds ratio [aOR] 0.66; 95% CI, 0.57–0.77), ectopic pregnancy (aOR 0.48; 95% CI, 0.34–0.69), cesarean delivery (aOR 0.90; 95% CI, 0.83–0.98), birth prior to 36 weeks’ gestation (aOR 0.89; 95% CI, 0.81–0.98), and delivery of an infant weighing <2,500 g (aOR 0.84; 95% CI, 0.71–0.89)."
Is screening colonoscopy more effective than annual FOBT in improving morbidity and mortality for colon cancer screening in adults?

Evidence-Based Answer
Colonoscopy and fecal occult blood testing (FOBT) have been associated with reduced cancer-specific mortality (SOR B: for colonoscopy, prospective cohort; SOR A: for FOBT, Cochrane review of RCTs) but there are no head-to-head comparative mortality data. Colonoscopy and FOBT have comparable detection rates for colorectal cancer (CRC) at 10 years, although colonoscopy identifies more adenomas and has higher complication rates (SOR B: RCTs).

The US Preventive Services Task Force (USPSTF) recommends screening adults aged 50–75 using FOBT every year, sigmoidoscopy every 5 years with FOBT every 3 years, or colonoscopy every 10 years (Grade A recommendation).¹

A 2007 Cochrane review of 4 RCTs including >300,000 patients assessed mortality outcomes for screening with FOBT.² Three trials performed biennial screening and 1 evaluated both annual and biennial screening.

Screening, compared with no screening, resulted in reduction of CRC mortality (4 trials, N=397,043; RR 0.84; 95% CI, 0.78–0.90) even when the relative risk was adjusted for patients who missed 1 or more FOBT (4 trials, N=397,043; RR 0.75; 95% CI, 0.66–0.84). No difference was noted in all-cause mortality (4 trials, N=397,043; RR 1.0; 95% CI, 0.99–1.0).²

A 2012 RCT of 57,404 patients compared one-time colonoscopy with fecal immunochemical testing (FIT) every 2 years in adults aged 50–69 years.³ No difference was noted in CRC detection between the colonoscopy group and the FIT group at 10-year follow-up (0.1% vs 0.1%; OR 0.99; 95% CI, 0.61–1.6). Colonoscopy had higher detection rates for both advanced adenomas (defined as adenomas measuring ≥10 mm with villous architecture, high-grade dysplasia, or intramucosal carcinoma) (OR 2.3; 95% CI, 2.0–2.7) and nonadvanced adenomas (OR 9.8; 95% CI, 8.1–12).

Rates of major complications—including bleeding, hypotension, bradycardia, perforation, and desaturation—were higher in the colonoscopy group than the FIT group (0.5% vs 0.1%; OR 4.8; 95% CI, 2.3-10). Comparative effectiveness results for preventing death from CRC are pending the completion of this 10-year trial.⁴

A 2013 prospective cohort trial assessed CRC incidence and mortality after screening colonoscopy in 88,902 patients who were followed for more than 22 years. Every 2 years, patients were asked whether they had undergone a colonoscopy, and for what reason.⁴

Patients who had at least 1 screening colonoscopy had lower risk of CRC mortality, compared with no screening (HR 0.32; 95% CI, 0.24–0.45). Risk of CRC was reduced with a 3- to 5-year screening colonoscopy interval (HR 0.40; 95% CI, 0.31–0.52) and with a 5- to 10-year screening colonoscopy interval (HR 0.52; 95% CI, 0.38–0.70) when compared to no screening.⁴

Andrew Patel, MD
Jack Wells, MD, MHA
University of Missouri
Columbia, MO


ERRATUM
In the February issue, the HDA article “Are dietary interventions effective in the treatment of multiple sclerosis?” (EBP. 2015; 18(2):12) listed authors incorrectly. The proper author citation is as follows:

Mark Wirtz, MD
Vi Song Tring, DO
Daniel Algert, MD
Jonathan Elliot, MD
Naval Hospital Pensacola
Pensacola, FL

Evidence You Can Trust
The Family Physicians Inquiries Network Consortium (FPIN) is a nonprofit 501(C)3 organization that operates for the exclusive purpose of providing research and education in the public interest. FPIN is the sole publisher of Evidence-Based Practice, produced as an educational service to members and subscribers worldwide.

The members of FPIN are deeply committed to providing accurate, unbiased, and evidence-based information that will help physicians provide better care to their patients.

You can trust that Evidence-Based Practice is completely independent of pharmaceutical industry influence.

You have our word on it.
Can metformin be used safely in a patient with elevated creatinine concentration?

**Bottom line**
Metformin is likely safe in patients with mild chronic kidney disease with reduced dosing and close monitoring (SOR: B, systematic review of cohort studies). However, caution should be advised in patients with multiple risk factors for lactic acidosis (SOR: C, case series).

**Evidence summary**
A Cochrane review (347 prospective comparative or observational cohort studies) assessed the risk of lactic acidosis in patients with type 2 diabetes taking metformin (70,490 patient-years) compared with other antidiabetic treatment or placebo (55,451 patient-years). The primary outcome assessed was death due to lactic acidosis or nonfatal lactic acidosis.

A limitation of this review was that renal insufficiency (defined as creatinine ≥1.5 mg/dL) was an exclusion criterion in 57% (191 of 347) of the studies evaluated. Other medical conditions associated with lactic acidosis were also frequently excluded: cardiovascular disease (excluded in 154 studies), liver disease (179 studies), pulmonary disease (46 studies), and age older than 65 years (40 studies).

No cases of lactic acidosis or death due to lactic acidosis appeared in any of the included studies.

A retrospective study (N=16) evaluated the correlation of metformin concentration to mortality in patients with metformin-associated lactic acidosis. Laboratory data were searched for patients with measured metformin concentrations and corresponding medical records were reviewed. Twelve patients had at least 1 risk factor for lactic acidosis (chronic renal failure, heart failure, chronic obstructive pulmonary disease, and alcohol abuse) before admission. Eight patients had previously diagnosed renal failure and an additional 6 patients had renal failure on admission.

No significant correlation was found between serum metformin and lactate concentrations (correlation coefficient 0.19; \(P=0.47\)) and mean lactate concentration in survivors and nonsurvivors did not differ (13.5 vs 14.5 mmol/L; \(P=0.68\)). Metformin accumulation due to renal failure occurred in 6 of the 16 cases (mean creatinine 9.0 mg/dL with metformin level 28.1 mg/L). These patients did not have cardiac or liver disease, and all 6 survived. The remaining 10 patients had less severe renal failure (mean creatinine 3.2 mg/dL and metformin level 5.3 mg/L) but more severe illnesses, such as cardiogenic shock or liver failure. Five of the 10 survived. Mortality was associated with more severe underlying disease; survivors actually had higher metformin concentrations overall (19 vs 2.9 mg/L; \(P=0.006\)).

**Recommendations**
The most current American Diabetes Association (ADA) Statement on the Management of Hyperglycemia indicates that a debate is ongoing about the use of metformin for patients with mild to moderate renal insufficiency. Contraindications to metformin in other countries are less proscriptive than those in the United States, generally allowing use among patients with a glomerular filtration rate (GFR) of a low as 30 mL/min, with dose reduction advised at 45 mL/min. Although the ADA does not provide outright support of this change, they do state that “given the current widespread reporting of estimated GFR, these guidelines appear very reasonable.”

---

**Spotlight on Pharmacy**

Can metformin be used safely in a patient with elevated creatinine concentration?

**Bottom line**
Metformin is likely safe in patients with mild chronic kidney disease with reduced dosing and close monitoring (SOR: B, systematic review of cohort studies). However, caution should be advised in patients with multiple risk factors for lactic acidosis (SOR: C, case series).

**Evidence summary**
A Cochrane review (347 prospective comparative or observational cohort studies) assessed the risk of lactic acidosis in patients with type 2 diabetes taking metformin (70,490 patient-years) compared with other antidiabetic treatment or placebo (55,451 patient-years). The primary outcome assessed was death due to lactic acidosis or nonfatal lactic acidosis.

A limitation of this review was that renal insufficiency (defined as creatinine ≥1.5 mg/dL) was an exclusion criterion in 57% (191 of 347) of the studies evaluated. Other medical conditions associated with lactic acidosis were also frequently excluded: cardiovascular disease (excluded in 154 studies), liver disease (179 studies), pulmonary disease (46 studies), and age older than 65 years (40 studies).

No cases of lactic acidosis or death due to lactic acidosis appeared in any of the included studies.

A retrospective study (N=16) evaluated the correlation of metformin concentration to mortality in patients with metformin-associated lactic acidosis. Laboratory data were searched for patients with measured metformin concentrations and corresponding medical records were reviewed. Twelve patients had at least 1 risk factor for lactic acidosis (chronic renal failure, heart failure, chronic obstructive pulmonary disease, and alcohol abuse) before admission. Eight patients had previously diagnosed renal failure and an additional 6 patients had renal failure on admission.

No significant correlation was found between serum metformin and lactate concentrations (correlation coefficient 0.19; \(P=0.47\)) and mean lactate concentration in survivors and nonsurvivors did not differ (13.5 vs 14.5 mmol/L; \(P=0.68\)). Metformin accumulation due to renal failure occurred in 6 of the 16 cases (mean creatinine 9.0 mg/dL with metformin level 28.1 mg/L). These patients did not have cardiac or liver disease, and all 6 survived. The remaining 10 patients had less severe renal failure (mean creatinine 3.2 mg/dL and metformin level 5.3 mg/L) but more severe illnesses, such as cardiogenic shock or liver failure. Five of the 10 survived. Mortality was associated with more severe underlying disease; survivors actually had higher metformin concentrations overall (19 vs 2.9 mg/L; \(P=0.006\)).

**Recommendations**
The most current American Diabetes Association (ADA) Statement on the Management of Hyperglycemia indicates that a debate is ongoing about the use of metformin for patients with mild to moderate renal insufficiency. Contraindications to metformin in other countries are less proscriptive than those in the United States, generally allowing use among patients with a glomerular filtration rate (GFR) of a low as 30 mL/min, with dose reduction advised at 45 mL/min. Although the ADA does not provide outright support of this change, they do state that “given the current widespread reporting of estimated GFR, these guidelines appear very reasonable.”

---

**REFERENCES**
1. A 27-year-old woman presents to your office with her second urinary tract infection (UTI) in 6 months. She asks about the use of cranberry juice to help prevent a UTI recurrence. You tell her that cranberry:
   - a. Will not be beneficial for her particular situation
   - b. Is recommended only if taken in high-dose capsule form
   - c. Is beneficial when taken immediately after intercourse
   - d. Has been shown to have more adverse effects than antibiotic prophylaxis

2. Regarding treatment of chronic vertigo, which of the following statements is correct?
   - a. Home exercises are less effective when combined with phone follow-up
   - b. The Epley maneuver significantly improves symptoms of benign paroxysmal positional vertigo
   - c. Adding activity restrictions after performing the Epley maneuver results in a large improvement of symptoms compared with the Epley maneuver alone
   - d. Home vestibular rehabilitation exercises are ineffective

3. An inter-pregnancy interval of <6 months after a miscarriage is associated with which of the following (compared with outcomes for conceptions after 6–12 months):
   - a. Higher likelihood of term delivery
   - b. Lower rate of miscarriage
   - c. Lower rate of ectopic pregnancy
   - d. All of the above

4. Which of the following statements is true about metformin use for patients with renal insufficiency?
   - a. A high metformin serum concentration in a patient with lactic acidosis is a poor prognostic indicator
   - b. Metformin is likely safe in patients with mild chronic kidney disease
   - c. Metformin can safely be used in patients with severe renal disease (glomerular filtration rate 15–29 mL/min)
   - d. Other comorbidities do not affect the mortality of metformin-associated lactic acidosis

5. A 66-year-old woman comes in to the office for a complete physical. She states she does not want any more Pap smears. What prior Pap history would let you know it is safe to stop?
   - a. Annual Pap smear cytologies for the last 2 years and both are negative
   - b. Three consecutive negative cytology results or 2 consecutive negative human papillomavirus (HPV) results within 10 years
   - c. One Pap and HPV test within 5 years and both are negative
   - d. It is not appropriate to stop without an assessment of her ongoing risk of HPV acquisition

6. Which of the following statements is true regarding unfractionated heparin (UFH) in deep vein thrombosis (DVT) prophylaxis in acutely ill, hospitalized patients?
   - a. BID dosing of UFH is less effective in preventing DVTs than TID dosing
   - b. There is no difference in the rate of DVTs between BID and TID dosing of UFH
   - c. TID dosing of UFH is associated with more major bleeding events than BID dosing
   - d. Guideline recommendations state TID dosing of UFH is preferred over BID dosing

7. Soy-protein based formula use in infants
   - a. Does not affect growth among healthy term infants
   - b. Increases the long-term risk of diabetes
   - c. Increases the long-term risk of breast cancer
   - d. Increases the long-term risk of cognitive dysfunction

8. Based on current data, screening colonoscopy is:
   - a. Comparable to fecal occult blood testing (FOBT) for reducing all-cause mortality
   - b. Superior to FOBT for reducing all-cause mortality
   - c. Comparable to FOBT for colorectal cancer detection
   - d. Superior to FOBT for colorectal cancer detection

For CME credit, return this test to: FPIN, 409 W. Vandiver Drive, Bldg. #4, Ste 202, Columbia, MO 65202 or fax to 573-256-2078. If you have questions, please contact Kerri Reynolds (ebp@fpin.org or call 573-256-2066).

Renew or Subscribe to EBP at www.fpin.org/subscribe or call 573-256-2066
FPIN is hitting the road again in 2015 with onsite workshops. Scholarships now available!

Back by popular demand, FPIN will be sending faculty presenters to residency programs across the country to offer faculty development and writing support. Plus - we’re offering scholarships to help with costs. Go to www.fpin.org/workshops and click on “Workshop Scholarship Application” for more information.

Questions? Email membership@fpin.org or call 573-256-2066.
Evidence-Based Answer

No, daily ZMA supplementation (90–120 mg zinc component) for 7 to 8 weeks in previously active men does not appear to increase serum testosterone levels (SOR: C, small conflicting studies with disease-oriented outcomes).

A 2004, placebo-controlled, double-blind RCT examined the effects of ZMA on serum testosterone and muscle mass. The trial enrolled 42 men between the ages of 18 and 50 years who had participated in resistance training 3 times weekly for at least 1 year and were not taking performance-enhancing supplements. Patients received either 4 ZMA tablets daily (120 mg zinc) or placebo while undergoing rigorous strength training for 8 weeks.

ZMA supplementation nonsignificantly increased serum zinc levels from baseline (from 11% to 17%; \(P=0.12\)). There were no differences in free testosterone (ZMA 1.7 pg/mL vs placebo 1.6 pg/mL; \(P=0.96\)), total testosterone (0.47 vs 0.12 ng/mL; \(P=0.50\)), and training performance (multiple variables) in the 2 groups. No significant clinical adverse effects were reported in either group. The study was underpowered to find even moderate changes in these outcomes.

A 2009 RCT randomized 14 healthy male volunteers who reported exercising 2.5 to 10 hours per week into ZMA supplementation or placebo groups for 8 weeks. Serum zinc levels were significantly raised from baseline after ZMA supplementation (0.29 ng/mL per week, \(P=0.031\)), but were unchanged in the placebo group. For both ZMA and placebo no significant changes were noted from baseline in free testosterone or total testosterone. This study was also underpowered to find moderate differences. The study did not examine muscle mass or athletic performance.

A double-blind placebo-controlled RCT studied the effect of ZMA on testosterone and muscle mass in college football players during spring training. Patients were randomized to take 3 ZMA tablets daily (90 mg zinc) or placebo for 7 weeks and were required to refrain from using other supplements during the study. Fifty-seven participants were enrolled, but only 27 completed the study (15 ZMA, 12 placebo) due to noncompliance with taking the supplement or obtaining blood tests.

ZMA was associated with a significant increase in serum zinc levels (ZMA 0.24 mcg/mL vs placebo 0.04 mcg/mL; \(P<0.001\)) and increases in serum free testosterone (42 vs 24 pg/mL; \(P=0.001\)) and total testosterone (184 vs 62 ng/mL; \(P<0.001\)). The makers of ZMA provided financial support for the research and 1 of the authors disclosed he had an equity interest in the company.

Evidence-Based Practice

(P=.81). The authors concluded vaginal Lactobacillus, with or without oral Lactobacillus, significantly reduced the incidence of recurrent VVC.\(^1\)

Another RCT randomized 46 women with a history of recurrent bacterial vaginosis or VVC to eat Lactobacillus-enriched yogurt (group 1) or pasteurized yogurt (group 2) daily for 2 months.\(^2\) A significant difference was noted in the vaginal isolation of Lactobacillus between the groups after 2 months of ingestion (>90% vs 25%, respectively; \(P<.05\)). However, no difference was noted in recurrent VVC infection rates (20% vs 28%, respectively; \(P=\)not significant).

An unblinded, crossover trial of 33 women with a history of recurrent VVC were randomized to eat Lactobacillus-containing yogurt once a day or a yogurt-free diet.\(^3\) After 6 months the groups switched.

A 3-fold decrease in VVC infections was observed in the group consuming the yogurt (a mean of 0.4 VVC infections in the yogurt group vs 2.5 in the control group; \(P=.001\)). Candidal colonization was also decreased in the yogurt group (a mean of 0.8 candidal colonizations in the yogurt group vs 3.2 in the control group, \(P=.001\)). However, only 13 women completed the study.\(^3\)

Dawn Talbert, DO
Sandra Minchow-Proffitt, MD
Mercy Hospital-Saint Louis FMRP
St. Louis, MO


Are computer-based interventions effective for decreasing symptoms in adolescents with major depression?

**Evidence-Based Answer**

One computer-based intervention (SPARX) is at least as effective as usual care for decreasing depressive symptoms in adolescents. Another intervention (MoodGYM) has limited efficacy for adolescent boys, but may be effective for teenage girls (SOR: \(B\), individual nonrandomized controlled trials).

A 2012 randomized controlled noninferiority trial compared a computer-based program (SPARX) with usual care in 187 adolescents 12–19 years old who sought treatment for depressive symptoms.\(^1\) Patients were excluded if they had a high risk of self-injury, cognitive impairments, or if they had received any treatment within the previous 3 months.

The patients in the SPARX group played a first-person adventure video game with 7 modules over 2 months. The modules taught coping skills, self-awareness skills, and problem-solving skills using cognitive-behavioral techniques. The patients in the control group received usual care, which could include face-to-face counseling or treatment from a primary care doctor. The primary outcome was score on the Child Depression Rating Scale-Revised (CDRS-R), a 103-point scale in which higher scores indicate more depression.\(^1\)

Patients in the SPARX group had a change in CDRS-R score from 44 at baseline to 29 after 5 months, while those in the control group changed from 43 to 30 (no measure of statistical significance was given for this comparison). The average change in CDRS-R score in the SPARX group was 10 (95% CI, 8.2–12) compared with 7.6 (95% CI, 5.4–9.8) in the control group with an average difference of 2.7 (95% CI, −0.31 to 5.8; \(P=.07\)) in the per-protocol analysis, showing that SPARX was not inferior to usual care.\(^1\)

A 2006 nonrandomized controlled trial compared a school-based, online cognitive-behavioral therapy course (MoodGYM) with a regular school curriculum for 78 ninth-grade boys.\(^2\) Participants in the MoodGYM group completed 5 interactive modules over 5 weeks. The modules included informative material and exercises on self-awareness, problem solving, and coping skills. The control group continued their usual curriculum, in which no specific depression discussion occurred. The primary outcome was the score on the Centre for Epidemiological Studies Depression Scale (CES-D), a 60-point scale in which a score of 16 or higher corresponds with depression. Participants followed up 1 and 4 months after the intervention.

Prior to the intervention, average CES-D score was 11 in both groups (\(P=.87\)). In the MoodGYM group, the mean change in CES-D score 4 months after the intervention was –1, compared with a mean change of –0.1 in the control group (scores estimated from figure, \(P=.27\)).\(^2\)

A similar nonrandomized controlled trial conducted in 2008 also compared the effectiveness of MoodGYM with a regular school curriculum for 157 adolescent girls.\(^3\) Participants in the MoodGYM group completed the same self-help curriculum modules over 6 weeks. The control group continued their usual personal development
curriculum, which was focused on nutrition at the time of the study. The primary outcome was measured using the CES-D scale, with the cutoff for depression at 16. Participants were assessed at preintervention, as well as at 6 and 20 weeks postintervention.

The study found that students in the MoodGYM group had a CES-D score of 18 at baseline and 13 at a 20-week follow-up, whereas those in the control group scored 19 at baseline and 16 at 20 weeks. Although no tests of statistical significance were reported for this outcome, the MoodGYM group appears to have had a decrease in CES-D score out of the depressive range.1

What is the best treatment for medication-induced rebound headaches?

Evidence-Based Answer
For patients with medication overuse headaches, abrupt withdrawal of the suspected offending agent with rescue medications or using a preventive medication (angiotensin II blockers, beta-blockers, antiepileptic drugs, or tricyclic antidepressants) at the time of withdrawal may decrease headache frequency (SOR: B, RCT).

A multicenter, open-label RCT of 56 patients evaluated treatment options for medication overuse headaches over a 12-month period.1 Patients were randomized into 3 groups: abrupt withdrawal with rescue medication (amitriptyline 10–25 mg, diclofenac 50 mg, naproxen 500 mg, or metoclopramide 20 mg up to 2 days/week), preventive treatment (angiotensin II blockers, beta-blockers, antiepileptic drugs, or tricyclic antidepressants, dosages not provided), and a control group that received no advice or medication.

Compared with baseline, preventive treatment (n=17) reduced headache days per month at 3 months (–7.2 days; 95% CI –2.7 to –12), 5 months (–7.3 days; 95% CI, –2.7 to –12), and 12 months (–10.3 days; 95% CI, –5.8 to –15). Abrupt withdrawal (n=20) also resulted in a decrease in headache days per month at 3 months (–4.2 days; 95% CI, –3.3 to –7.4), 5 months (–4.8 days; 95% CI, –1.3 to –8.2), and 12 months (–5.1 days; 95% CI, 0.9 to –9.3). The control group (n=19) did not have a reduction in headache days compared with baseline (3 months: –1.6 days; 95% CI –5.1 to 1.8; 5 months: –2.1 days; 95% CI, –5.2 to 0.8).1

In a 4-year follow-up study, 83% of the original study participants (N=50) were reevaluated.2 While two-thirds of the patients maintained at least a 50% reduction in headache frequency, there was no correlation with the type of early intervention.

The 2011 European Federation of Neurological Societies (EFNS) Headache Panel expert guidelines for management of medication overuse headaches recommended the abrupt withdrawal of the offending medication.2 Tapered withdrawal was recommended for opioids, benzodiazepines, and similar addictive medications. The guideline stated that no studies had directly compared abrupt versus tapered withdrawal, so recommendations were based on limited evidence.

Trials reviewed by the guideline indicated topiramate decreased chronic migraine headache frequency per month compared with placebo (–3.5 vs –0.2; P<.05), although 75% of the topiramate group reported adverse effects. Other small open-label trials reviewed by the guideline suggested preventive treatment with topiramate and valproic acid might benefit. Results with oral corticosteroids were conflicting, with benefit reported from prednisone and prednisolone in a large open-label trial and a small proof-of-concept study, but the only double-blinded RCT (N=97) investigating the use of oral prednisolone during the first 6 days after medication withdrawal showed no significant benefit. Other nonplacebo-controlled studies reviewed suggested amitriptyline (10–50 mg), naproxen (500 mg), or sumatriptan (subcutaneous injection) might be effective for withdrawal headache symptoms.3

Gregory Eigner, MD
Bob Karp, MD
Marianne Cumming, MD
Fort Wayne Medical Education Program
Fort Wayne, IN