Evidence-Based Practice
Answering clinical questions with the best sources

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IN THE NEWS

AHRQ report targets arthritis medication safety

The Agency for Healthcare Research and Quality (AHRQ) recently released a Comparative Effectiveness Review that summarizes the evidence concerning the safety and efficacy of analgesics used to treat arthritis. The report was researched and written by the Oregon Evidence-Based Practice Center and attempts to address the bewildering array of clinical trials and systematic reviews published on the topic.

Epidemiology

Osteoarthritis is the most common form of arthritis in adults. Estimates are that 6% of the adult population older than 30 has symptomatic osteoarthritis of the knee. The prevalence rises with age, increasing between 2- and 10-fold between the ages of 30 and 65. Arthritis of all forms is estimated to cost the equivalent of 2% of the gross domestic product, with more than half the costs due to lost work productivity.

Interventions

Any discussion of arthritis therapy with a physician will likely include a discussion of nonsteroidal anti-inflammatory drugs (NSAIDs). Although widely used, NSAIDs resulted in an estimated 32,000 hospitalizations and 3,200 deaths each year throughout the 1990s, primarily due to gastrointestinal (GI) hemorrhaging. In an attempt to mitigate these outcomes, evidence has supported the co-administration of NSAIDs with misoprostol (Cytotec®) or proton pump inhibitors. More recently, a new class of NSAIDs—the cyclooxygenase-2 (COX-2) inhibitors—has been specifically developed to have less adverse impact on the GI mucosa. Unfortunately, several members of this class (rofecoxib [Vioxx®] and valdecoxib [Bextra®]) have been pulled from the market because of an association with cardiovascular problems, primarily myocardial infarction (MI). This finding has cast suspicion over the entire class of medications.

continued
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Research

To better assess the risks and benefits of these drugs, the AHRQ performed a systematic review that identified 2,665 trials or meta-analyses of arthritis therapy and selected those that compared 1 drug to another drug, therapy, or placebo. Cohort and case-control studies that included more than 1,000 patients addressing serious GI or cardiovascular endpoints were also included. A total of 351 publications met inclusion criteria. Key findings of the AHRQ review are shown in the Table. Among the pivotal research papers included in the review were the VIGOR and TARGET trials and the Kearney meta-analysis.

VIGOR trial

The VIGOR trial was the first to document a potential increase in cardiovascular risk due to COX-2 inhibitors. In this trial, 8,076 older adults with rheumatoid arthritis were randomized to either 50 mg rofecoxib daily or 500 mg naproxen twice daily and were followed an average of 9 months.

The researchers recorded 2.1 adverse GI events per 100 patient-years with rofecoxib compared with 4.5 with naproxen (hazard ratio [HR] 0.5; 95% confidence interval [CI], 0.3–0.6; P < .001). But 0.4% of the rofecoxib group also had MIs compared with 0.1% of the naproxen group (HR 4; 95% CI, 1.4–10; number needed to treat [NNT] with rofecoxib for 1 additional MI, 333).

Later researchers determined that 3 additional cardiovascular events had occurred in the rofecoxib group that had not been included in the main report. Subsequent blinded adjudication of the VIGOR data showed that 1 in every 90 patients taking rofecoxib had a serious thrombotic event (defined as an MI, stroke, unstable angina, transient ischemic attack, or cardiac arrest). There was 1 serious thrombotic event for every 212 patients taking naproxen.

TARGET trial

The TARGET trial evaluated 18,325 patients age 50 and older with osteoarthritis randomized to lumiracoxib (a COX-2 inhibitor not currently avail-
able in the United States) 400 mg once daily, naproxen 500 mg twice daily, or ibuprofen 800 mg 3 times daily for 1 year.\textsuperscript{3,4} Patients taking aspirin for cardiac protection were not excluded.

Therapy with lumiracoxib was associated with fewer upper GI complications than the other NSAIDs (HR 0.34; 95% CI, 0.22–0.52; \(P < .0001\), NNT with lumiracoxib for 1 less GI event 167). However, in the subset of patients concomitantly taking aspirin, no statistically significant difference was noted in GI complications. Slightly more MIs were recorded in the lumiracoxib group compared with the other NSAIDs (23 vs 17 for other NSAIDs) but the difference was not statistically significant (HR 1.31; 95% CI, 0.70–2.45; \(P = .4\)).

**Kearney meta-analysis**

The Kearney meta-analysis\textsuperscript{5} identified prospective randomized trials of the use of COX-2 inhibitors compared with nonselective NSAIDs or placebo for patients with arthritis. A total of 138 trials were included, representing 145,373 participants. Pooling results on all COX-2 inhibitors found an increased rate of MI compared with placebo (HR 1.86; 95% CI, 1.33–2.59; \(P = .0003\)) and compared with all other NSAIDs (HR 1.53; 95% CI, 1.19–1.97; \(P = .0009\)). Importantly, no difference was noted in MI rates between COX-2 inhibitors and other NSAIDs when naproxen studies were removed, suggesting that non-naproxen NSAIDs (particularly ibuprofen and diclofenac in high doses) might also increase cardiovascular risk.

The AHRQ report also separately discussed data concerning celecoxib (Celebrex\textsuperscript{®}), the only COX-2 inhibitor currently available in the United States. Early studies showed no adverse cardiovascular outcomes, but no clear GI advantage either; later meta-analyses more convincingly documented GI protection, but also noted an increase in MIs.\textsuperscript{1} The authors stated that the newest data raise “additional questions about [celecoxib’s] appropriate use.”

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**From the Editor**

**Why the bias in favor of significant differences?**

Dear EBP Readers,

Every few years, someone with a great love of mathematics decides to write a paper about the statistical methods used in medical research papers. The results are usually sobering if a bit predictable: medical researchers (and—gasp!—journal editors) are not particularly good statisticians.

Most recently, a fellow by the name of Peter Gøtzsche\textsuperscript{1} reviewed all randomized controlled trials (RCTs) in PubMed from 2003 that reported relative risks or odds ratios and compared them with a random sample of cohort and case-control studies to see if the \(P\) values in the abstracts were “believable.”

In the 620 papers reviewed, 86% of the RCTs, 93% of the cohort studies, and 93% of the case-control studies presented “statistically significant” results in the abstracts. Significant results were often derived from subgroup analysis, but this fact was not mentioned in the abstract 98% of the time. Published \(P\) values were between 0.04 and 0.05 5 times as often as between 0.05 and 0.06. Mr. Gøtzsche concluded that “significant results in abstracts should generally be disbelieved.” This statement is unsettling for the physician striving to practice evidence-based medicine.

Why is there a bias in favor of significant differences?

My colleague, Dr. Bernard Ewigman, Professor and Chair of the Department of Family Medicine at the University of Chicago, tells me that the answer is “the tyranny of the ubiquitous \(P\) value.” As you recall, the tolerable risk that an association is due to random chance was set at .05 by statisticians, not clinicians. Can we really say that a clinical finding with a \(P = .051\) is “not significant,” whereas one with a \(P = .049\) is “significant”? Medical research and medical care decisions are far more complex than that. There is a real danger of prematurely discarding a large portion of our research just because the \(P\) value is a smidge “over the line.”

Banning \(P\) values would certainly reduce the overzealous pursuit of "significant" findings in subgroup analyses by competitive academic authors. It might also reduce the tendency of naïve editors to equate “publishability” with statistical significance.

Instead, medical research might more commonly use confidence intervals. And that is exactly what we try to do here at Evidence-Based Practice, whenever we can find them.

Regards,

Jon O. Neher, MD

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Help Desk

Is mobile phone use associated with increased risk of brain tumors?

Evidence-Based Answer
Although the investigations into this question have been case-control studies, and hence subject to significant bias, the accumulating evidence from multiple populations does not support the idea that mobile phone use places individuals at increased risk of brain tumors. (SOR B, based on several case-control studies.)

In a study of 469 men and women aged 18 to 80 years with primary brain cancer and 422 matched controls without brain cancer, no association was found for history, frequency, or duration of mobile phone use. Another case-control study matched 782 cases (489 gliomas, 197 meningiomas, 96 acoustic neuromas) with 799 controls, and found no association with frequency or duration of mobile phone use, nor with specific subtypes of brain tumors. Subsequent studies have had similar findings. A recently published analysis examined whether an association exists between glioma and mobile phone use for specific variables such as development of ipsilateral high-grade astrocytoma and rural versus urban use, these findings have not been replicated by subsequent research. Despite the limitations inherent to the case-control design, the weight of evidence argues against a significant association between developing brain tumors and having a history of mobile phone use.


What are the best tests for diagnosing sarcoidosis?

Evidence-Based Answer
Transbronchial lung biopsy is the best method for collecting biopsy specimens to prove a patient has noncaseating granulomatous disease of the lung. But no single additional finding reliably confirms sarcoidosis. Increased serum angiotensin-converting enzyme (ACE) levels, gallium-67 scanning, and CD4-to-CD8 ratios in bronchoalveolar lavage fluid are not specific enough to independently confirm the diagnosis. (SOR C, based on expert opinion.)

Sarcoidosis is a multisystem disease of unknown origin characterized by noncaseating granulomas. Review articles on sarcoidosis advocate a 4-step process to making the diagnosis:

1. Transbronchial lung biopsy
2. Serum angiotensin-converting enzyme (ACE) levels
3. Gallium-67 scanning
4. CD4-to-CD8 ratios in bronchoalveolar lavage fluid
1. Demonstrate noncaseating granulomas on biopsy
2. Establish clinical correlations between the pathology and patient symptoms
3. Obtain a complete medical, occupational, and environmental history
4. Rule out other possible diagnoses

As sarcoidosis is a diagnosis of exclusion and the differential diagnosis is extensive, the diagnostic pathway is not standardized. One review cites several studies that indicate that the more thoroughly other causes of granulomatous disease are investigated, the less often sarcoidosis is diagnosed.¹

In persons with pulmonary involvement, transbronchial lung biopsy is usually recommended because of higher yield (up to 90% when multiple biopsies taken) and lower rates of complications than other methods.¹²⁴ Other acceptable methods include needle aspiration, bronchoalveolar lavage, open-lung biopsy, and mediastinoscopy.

The more organs in which the pathologic lesions can be found, the more likely the diagnosis.³ A thorough history and examination may identify more biopsy sites, particularly cutaneous lesions. In addition, chest radiography, electrocardiography, slit-lamp ophthalmologic examination, and a chemical panel to evaluate hepatic and renal function are recommended.¹

Clinical features that support the diagnosis of sarcoidosis include age younger than 40 years, Löfgren syndrome (erythema nodosum, hilar adenopathy, and arthralgias), lupus pernio (indurated plaques or papular skin lesions), and uveitis.²³⁵

Histologic specimens should be examined thoroughly to rule out neoplastic lesions or necrotic (caseating) granulomas. Cultures and stains for fungi and mycobacteria are indicated.

Other tests to consider depending on the clinical presentation include tests for antineutrophil cytoplasmic antibodies for Wegener’s granulomatosis, antimitochondrial antibodies for primary biliary cirrhosis, or a beryllium lymphocyte-proliferation test for chronic beryllium disease.¹

Other examinations that may support a diagnosis of sarcoidosis but lack sensitivity and specificity include a CD4-to-CD8 ratio higher than 3.5 in bronchoalveolar lavage fluid (associated with a positive predictive value of 76%, a negative predictive value of 85%, a specificity of 94%, and a sensitivity of 53%).⁴ Gallium-67 scanning may support the diagnosis in a small subset of patients. Elevation of ACE twice the upper limit of normal lends support but is not specific, because other granulomatous disease may cause this ACE elevation.²⁴

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Which is better for treating tennis elbow: corticosteroid injections or physical therapy?

Evidence-Based Answer

For patients with tennis elbow (lateral epicondylitis), randomized trials have consistently shown that although corticosteroid injections produce better results than physiotherapy in the short term (6 weeks), over the long term, patients do better when initially started on physiotherapy. (SOR A, based on multiple RCTs.)

In 1 trial, 185 patients with tennis elbow of at least 6 weeks’ duration were randomly assigned to receive corticosteroid injection (10 mg triamcinolone acetonide in 1 mL 2% Xylocaine) or physiotherapy (9 sessions of pulsed ultrasound, deep friction massage, and an exercise regimen), or were prescribed a “wait-and-see” approach.¹ Patients in the wait-and-see group were allowed to use over-the-counter analgesics as needed. The primary outcomes were patient-assessed symptom and disability ratings, and clinical assessments performed by physiotherapists who were unaware of group allocation. Assessments were performed at 3, 6, 12, 26, and 52 weeks.

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Success (complete or nearly complete recovery) was much more common in the corticosteroid injection group than either of the other 2 groups at 6 weeks, but at 52 weeks, only 69% of participants in the corticosteroid injection group were symptom-free, compared with 91% of the physiotherapy group and 83% of the wait-and-see group. The MANOVA for repeated measures showed that the course of symptoms was significantly different ($P < .001$) in all 3 intervention groups.

A subsequent trial has confirmed these findings. $^2$ A total of 198 patients who had tennis elbow for at least 6 weeks were randomly assigned to corticosteroid injection (10 mg triamcinolone acetonide in 1 mL 1% lidocaine), physiotherapy (eight 30-minute sessions of elbow manipulation over a 6-week period, plus therapeutic exercise), or to the “wait-and-see” approach. The primary outcomes were global improvement (self-assessment), pain-free grip force, and a rating of severity by an assessor who was unaware of group allocation. Analysis was by intent-to-treat.

At 6 weeks, more participants who had received corticosteroid injection were described as having successful outcomes than persons in the physiotherapy group (78% vs 65%; relative risk reduction [RRR] favoring injection = 0.7; 95% CI, 0.4–0.9; number needed to treat [NNT] = 7). But by 12 weeks, only 45% of participants in the injection group described their treatment as successful, compared with 76% in the physiotherapy group (RRR favoring physiotherapy = 0.4; 95% CI, 0.1–0.7; NNT = 3). And at 1 year, 68% in the injection group compared with 94% in the physiotherapy group reported successful treatment (RRR favoring physiotherapy = 0.3; 95% CI, 0.1–0.5; NNT = 4).


**Should children be screened for diabetes?**

**Evidence-Based Answer**

The American Diabetes Association (ADA) recommends screening for type 2 diabetes mellitus among high-risk children beginning at 10 years of age or the onset of puberty, whichever is earlier. (SOR C, based on expert opinion.) It is unclear, however, if such screening reduces long-term complications from the disease.
Help Desk CONTINUED

Data from a 2001 population-based, observational study of physician-diagnosed diabetes among youth less than 20 years of age revealed a crude prevalence of 1.82 cases per 1,000 (95% CI, 1.78–1.87 cases per 1,000 youth). The incidence of type 2 diabetes in children is increasing and accounts for up to 45% of all newly diagnosed cases.

An ADA consensus statement developed in 2000 by a panel of experts specializing in diabetes among children recommends screening at-risk children for type 2 diabetes mellitus. Criteria for screening include body mass index higher than the 85th percentile for age and sex, or weight more than 120% of ideal, along with 2 other risk factors. Risk factors include:

- A family history of type 2 diabetes
- Signs of insulin resistance or conditions associated with insulin resistance (ie, acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovarian syndrome)
- Maternal history of gestational diabetes
- Being a member of an ethnic group at increased risk (ie, African American, Native American, Hispanic American/Latino, Asian American, and Pacific Islander)

For overweight children with 2 additional risk factors, the recommendation is that screening begin at 10 years of age or the onset of puberty, whichever is earlier. The recommended test is a fasting plasma glucose with repeat screening every 2 years.

The fasting plasma glucose test and 2-hour oral glucose tolerance test have been shown to have acceptable sensitivity and specificity for screening high-risk children. A fasting plasma glucose concentration of 126 mg/dL or higher (fasting = no caloric intake for at least 8 hours) is more commonly used secondary to lower cost and greater convenience. Although the US Preventive Services Task Force found good evidence that available screening tests can accurately detect type 2 diabetes during an early, asymptomatic phase in adults, evidence is limited in reference to children, and the Task Force made no formal recommendation for or against routine screening in this population.

A retrospective chart review of electronic health data (2002–2004) from more than 7,700 patients aged 10 to 19 years from an urban primary care clinic in Boston revealed higher screening rates among patients meeting ADA screening criteria. However, less than half of those adolescents meeting criteria for screening were screened. Further evidence is necessary to determine if screening for diabetes among pediatric patients decreases morbidity and premature mortality associated with diabetes.

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Is tacrolimus (Protopic®) effective for treating atopic dermatitis?

Evidence-Based Answer
Tacrolimus ointment (Protopic) has been approved by the US Food and Drug Administration for the treatment of atopic dermatitis. Although the results of multiple randomized controlled trials (RCTs) show superiority over placebo, with the 0.1% ointment having an effect similar to high-potency corticosteroids, the agent should not be considered a first-line treatment. This recommendation is due to the lack of long-term trials, the absence of any long-term safety benefit compared with corticosteroids, and concerns with respect to possible cancer risk. (SOR A, based on a systematic review.)

Authors of a systematic review identified 25 RCTs that compared the use of tacrolimus or pimecrolimus with either placebo or topical corticosteroids among 6,897 patients with atopic dermatitis. Using the outcome of clearing or near clearing (90% reduction) of the rash, the best results were achieved for tacrolimus 0.1% ointment after 12 weeks (Table 1). High-potency tacrolimus (0.1%) was found to be equivalent to high-potency corticosteroids.

The most common adverse event associated with the use of tacrolimus was a sensation of skin
This occurred significantly more frequently in the tacrolimus groups compared to placebo, low-potency corticosteroids, and high-potency corticosteroids (for all comparisons, \( P < .05 \)). Additionally, the FDA has recently required a boxed warning to be included in the labeling for tacrolimus, due to a possible cancer risk based on animal studies.\(^2\)

Due to the lack of longer-term studies, the absence of trials evaluating the efficacy of tacrolimus in clinically important populations such as steroid-resistant cases, and the high incidence of adverse events, this agent should not be considered for first-line therapy. This recommendation is consistent with a recently revised labeling requirement, which also states that it should not be used for children younger than 2 years.\(^3\)

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**TABLE 1**

<table>
<thead>
<tr>
<th>Outcome after treatment for atopic dermatitis(^1)</th>
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</thead>
<tbody>
<tr>
<td><strong>Relative rate of outcome</strong></td>
</tr>
<tr>
<td><strong>Tacrolimus vs placebo(^1)</strong></td>
</tr>
<tr>
<td>0.03% ointment vs vehicle (N=656)</td>
</tr>
<tr>
<td>0.1% ointment vs vehicle (N=655)</td>
</tr>
<tr>
<td><strong>Tacrolimus vs low-potency topical corticosteroid</strong></td>
</tr>
<tr>
<td>0.03% ointment vs 1% hydrocortisone acetate (N=790), 2 trials, at 3 weeks</td>
</tr>
<tr>
<td>0.1% ointment vs 1% hydrocortisone acetate (N=371), 1 trial, at 12 weeks</td>
</tr>
<tr>
<td><strong>Tacrolimus vs high-potency topical corticosteroid(^1)</strong></td>
</tr>
<tr>
<td>0.03% ointment vs 0.1% hydrocortisone butyrate (N=379)</td>
</tr>
<tr>
<td>0.1% ointment vs 0.1% hydrocortisone butyrate (N=377)</td>
</tr>
</tbody>
</table>

*Outcome was defined as clearing or near clearing (90% reduction) of the rash.
\(^{1}\)Three trials, results at 12 weeks.
\(^{2}\)One trial, results at 12 weeks.
CI=confidence interval.

**TABLE 2**

<table>
<thead>
<tr>
<th>Incidence of skin burning(^1)</th>
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</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td><strong>Tacrolimus vs placebo</strong></td>
</tr>
<tr>
<td>Tacrolimus, 0.03%</td>
</tr>
<tr>
<td>Tacrolimus, 0.1%</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Tacrolimus vs low-potency topical corticosteroid</strong></td>
</tr>
<tr>
<td>Tacrolimus, 0.03% vs low-potency corticosteroids</td>
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<tr>
<td>Tacrolimus, 0.1% vs low-potency corticosteroids</td>
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<tr>
<td><strong>Tacrolimus vs high-potency topical corticosteroids</strong></td>
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<tr>
<td>Tacrolimus, 0.03% vs high-potency corticosteroids</td>
</tr>
<tr>
<td>Tacrolimus, 0.1% vs high-potency corticosteroids</td>
</tr>
</tbody>
</table>

For all comparisons, \( P < .05 \).

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Trial of labor after cesarean section (TOLAC) with an undocumented uterine scar

The cesarean rate in the United States has risen from 5% in 1970 to 26% in 2002. In 2002, more than 87% of women with a previous cesarean had a repeat cesarean. As an alternative, women may opt for a trial of labor after cesarean (TOLAC) if they have a transverse lower uterine scar. The main risk of a TOLAC is uterine rupture. The risk of uterine rupture is 0.2% to 1.5% for a transverse lower uterine incision and 4% to 9% for a classical vertical uterine incision. Because of the higher risk with a vertical scar, TOLAC is considered contraindicated in this setting.

Unfortunately, the uterine scar direction cannot be inferred from the skin incision. Operative reports from Mexico and elsewhere may refer to a Kerr incision, so-named because the transverse lower uterine segment incision was made popular by Monro Kerr in 1926. A vertical skin incision with a Kerr uterine incision would not preclude a TOLAC. Conversely, a Pfannenstiel (transverse) skin incision may be accompanied by a classic (vertical) T or J uterine incision, which would contraindicate a TOLAC.

Some experts feel that a uterine scar can usually be inferred by the indication for the previous cesarean delivery. A vertical uterine incision is more likely to be used for emergent and preterm operative deliveries and operative deliveries for transverse lie.

To date, no large randomized controlled trials (RCTs) have been published that have assessed the safety of a TOLAC with an undocumented uterine scar. Two case series demonstrated that successful vaginal birth after cesarean and uterine rupture rates were similar for women with and without documented uterine scars. In a record review of 300 women with an unknown uterine scar and 88 with a transverse lower uterine incision, the rate of vaginal delivery and maternal and fetal outcomes were not statistically different. In another record review of 97 women with an unknown uterine scar and 204 women with a transverse lower uterine incision, estimated blood loss of more than 1,000 mL, maternal fever, uterine scar separation, perinatal mortality associated with a TOLAC, and 5-minute Apgar score less than 7 showed no statistically significant difference.

One small RCT looked at the safety of augmentation for women in latent labor who had a previous cesarean with an unknown uterine scar. Women with a history of 1 or 2 previous cesareans who presented at term with contractions were randomized to an intervention or nonintervention group. The intervention group (N=96) was augmented with oxytocin if spontaneous progression to active labor did not ensue. The nonintervention group (N=101) was discharged home if they did not progress spontaneously to active labor. No statistically significant difference was noted in the length of active labor or the cesarean delivery rate for the 2 groups, but uterine rupture occurred in 5 women receiving oxytocin and in none of the women in the nonintervention group.

Based on current evidence, it is considered acceptable to offer a TOLAC to a woman with an undocumented uterine scar. Patients and physicians should be aware of the increased risk of uterine rupture with augmentation.

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REFERENCES
Clinical Question

In patients with chronic kidney disease, anemia develops due to erythropoietin deficiency. Symptoms of fatigue, impaired exercise tolerance, dizziness, angina, and decreased cognition decrease patients’ quality of life. An erythropoiesis-stimulating agent is often administered to increase hemoglobin concentrations and improve quality of life. Initial observational studies found that raising hemoglobin concentrations decreased cardiovascular risk and was safe. Yet other studies indicated that normalizing hemoglobin concentrations did not improve ventricular function or reduce mortality.

The most recent guidelines published by the National Kidney Foundation recommend target hemoglobin concentrations between 11.0 and 13.0 g/dL in patients with chronic kidney disease regardless of whether or not they are receiving dialysis. The upper limit of this range is based on observational studies, the majority of which were performed in patients receiving dialysis. Clinical trials to determine optimal hemoglobin concentrations for patients treated with an erythropoiesis-stimulating agent who are not receiving dialysis have been lacking. Two clinical trials have been performed to address this issue.

The Data

CHOIR trial

The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial was a 16-month, open-label, randomized trial of 1,432 patients with anemia due to chronic kidney disease. All patients had to be at least 18 years old, have stage 3 or 4 chronic kidney disease, and not currently be receiving dialysis. Baseline hemoglobin concentrations were less than 11.0 g/dL in all subjects. Patients were treated with recombinant human erythropoietin (epoetin alfa) to achieve target hemoglobin concentrations of 11.3 g/dL (low hemoglobin group, N=717) or target concentrations of 13.5 g/dL (high hemoglobin group, N=715). The primary endpoint was time to a composite of death, myocardial infarction, hospitalization for congestive heart failure (without renal-replacement therapy), or stroke. Patients in the high hemoglobin group only reached a mean hemoglobin level of 12.6 g/dL despite the target of 13.5 g/dL, whereas patients in the low hemoglobin group reached their target with a mean hemoglobin level of 11.3 g/dL.

A total of 125 endpoint events occurred in the high hemoglobin group compared with 97 in the low hemoglobin group (hazard ratio, 1.34; 95% CI, 1.03–1.74; P=.03). Significantly more patients in

The Bottom Line

Target hemoglobin concentrations found in guidelines for treating the anemia of chronic kidney disease in patients not on dialysis are not supported by solid evidence and may be too high.

Key Points

• In patients with anemia caused by chronic kidney disease (not on dialysis) and treated with an erythropoiesis-stimulating agent, normalizing the hemoglobin concentration does not improve cardiovascular risk. Conflicting evidence suggests cardiovascular morbidity may be increased.
• The evidence is conflicting regarding improvement in quality of life with treatment of anemia with erythropoiesis-stimulating agents in this setting.

Erythropoiesis-stimulating agents in chronic kidney disease: How low can we go?
Patients had to be at least 18 years of age and have baseline hemoglobin concentrations between 11.0 and 12.5 g/dL. A total of 603 patients were randomized to receive treatment with subcutaneous erythropoietin (epoetin beta) to achieve target hemoglobin concentrations in the normal range (13.0–15.0 g/dL, N=301) or the subnormal range (10.5–11.5 g/dL, N=302). The primary endpoint was time to first cardiovascular event defined as sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalization, complication of peripheral vascular disease, or cardiac arrhythmia resulting in hospitalization.

An insignificant difference in the primary endpoint was observed in the 3-year open-label, randomized study. A total of 105 primary events occurred during the trial with 58 occurring in the normal hemoglobin group and 47 occurring in the subnormal hemoglobin group (P = .20). Significantly more patients in the normal hemoglobin group had hypertension than in the subnormal hemoglobin group (30% vs 20%, P = .005). All quality-of-life measures were significantly better in the normal hemoglobin group compared with the subnormal hemoglobin group.

**Summary**

Based on these recent trials, higher hemoglobin concentrations in chronic kidney disease patients who are not on dialysis has not been shown to decrease cardiovascular risk, and may actually be associated with an increased risk. Lower target hemoglobin concentrations of 11.0 to 12.0 g/dL should be considered in this patient population. Evidence to support the quality-of-life benefits associated with correction of anemia in chronic kidney disease patients not receiving dialysis remains inconclusive.

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Cara Liday, PharmD, CDE
Rex W. Force, PharmD, BCPS
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**REFERENCES**


**CME CREDIT**

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Michigan State University College of Human Medicine and the Family Physicians Inquiries Network (FPIN). The Michigan State University College of Human Medicine is accredited by the ACCME to provide continuing medical education for physicians.

It is estimated that this educational activity will require 3 hours to complete.

**Credit Designation statement**

Michigan State University, College of Human Medicine, designates this educational activity for a maximum of three (3) hours in Category 1 credit toward the AMA Physician’s Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

The learning objectives of the Evidence-Based Practice newsletter are to become knowledgeable about evidence-based solutions to commonly encountered clinical problems, to understand how groundbreaking research is changing the practice of family medicine, and to become conversant with balanced appraisals of drugs that are currently being marketed to physicians and/or consumers.

The editors of this educational material may review studies that discuss commercial products or devices as well as the unapproved/investigational use of commercial products/devices. The editors of this educational material report that they do not have significant relationships that create, or may be perceived as creating, a conflict relating to this educational material.

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Summary

In its summary, the AHRQ report concludes that there is good evidence that all NSAIDs are equally effective at reducing arthritis pain. However, it cautions that each NSAID likely has individual GI and cardiovascular toxicity independent of class. Naproxen was singled out as having the best cardiovascular profile (other than aspirin) according to current data. However, the report concluded that enough gaps exist in the evidence that making a solid determination of the balance of benefits and harms for any of these agents is impossible.

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University of Washington

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Do Nasal Decongestants Relieve Cold Symptoms?

We all know the symptoms of a cold: sneezing, congestion, runny nose, coughing, sore throat, and congestion that can last 1 to 2 weeks. When we catch a cold virus, glands in our nose and sinuses that normally produce only a small amount of mucus may produce up to 2 quarts of mucus a day! Mucus drains down the back of the throat, causing soreness, scratchiness, and coughing.

People try all sorts of therapies for cold symptoms. Certain cold remedies, called decongestants, relieve nasal swelling and congestion by constricting blood vessels. Decongestants are available in pill form (pseudoephedrine and phenylephrine) and as a nasal spray (oxymetazoline). They relieve symptoms slightly for a day or 2. Unfortunately, the congestion can quickly return with even more swelling as the medication wears off. Continuous use of decongestant sprays in particular can lead to a dependence on them, resulting in increased congestion and discomfort.

Another group of medicines people sometimes take for cold symptoms are antihistamines (diphenhydramine and chlorpheniramine, among others). They work by blocking the body’s response to allergies. Although allergies and colds often have the same set of symptoms (stuffy nose, runny eyes, cough, etc), antihistamines are not useful for colds and can actually be excessively drying or cause drowsiness.

Many commonly sold nonprescription cold medicines are “cocktails” of several drugs combined in 1 pill or liquid. They may contain aspirin, acetaminophen, or ibuprofen (for aches and pains or fever), a decongestant, an antihistamine, something for cough, alcohol, and other chemicals.

Although the decongestant in a combination product may offer short-term help, the other included compounds may not be needed or may actually be harmful. Some better strategies to relieve the congestion might be to do the following:

- Stand in a hot shower or lean over a container of steaming water for 10 to 15 minutes. Use a towel to make a tent over your head to concentrate the steam
- Drink plenty of liquids to help thin the mucus and make it easier to swallow or blow out
- Use saline nasal sprays, which help cleanse the passage and relieve congestion
- Get plenty of rest and sleep to help your body rid itself of the cold virus
- Avoid “combination” cold medications. If you want to try a decongestant take it alone, not in a drug “cocktail” with other medications

Decongestant pills and liquid medications should never be used for children younger than the age of 2 and should be used with extreme caution in older children.

For more information

Common Cold (Medline Plus)

Decongestants: OTC Relief for Congestion (American Academy of Family Physicians)
http://familydoctor.org/859.xml

Runny Nose or Stuffy Nose? Here’s What to Do (Mayo Foundation for Medical Education and Research)
http://www.mayoclinic.com/health/runny-nose/ID00006
1. For treatment of tennis elbow, when is corticosteroid injection superior to physiotherapy?
   a. At 6 weeks
   b. At 12 weeks
   c. At 1 year
   d. All of the above

2. High-potency tacrolimus is equivalent to which of the following agents for treating atopic dermatitis?
   a. Placebo
   b. Low-potency corticosteroids
   c. High-potency corticosteroids
   d. All of the above

3. All of the following statements are supported by “good” quality evidence according to the Agency for Healthcare Research and Quality’s Comparative Effectiveness Review of arthritis medications except
   a. Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are as effective as cyclooxygenase-2 (COX-2) inhibitors for arthritis pain
   b. Aspirin is as effective as nonselective NSAIDs for arthritis pain
   c. All nonselective NSAIDs increase the risk of gastrointestinal bleeding about equally
   d. Aspirin use is associated with a reduction of heart attack risk

4. What is another name for a transverse lower uterine segment incision during a cesarean delivery?
   a. Pfannenstiel
   b. Kerr
   c. T
   d. J

5. The association between brain tumors and mobile phone use?
   a. Is most strongly found for long-term users
   b. Is most strongly found for analog versus digital phone users
   c. Has not been demonstrated by most studies
   d. Is only significant for gliomas

6. All of the following are considered risk factors for the development of type 2 diabetes mellitus in children except
   a. Family history of type 2 diabetes mellitus
   b. Acanthosis nigricans
   c. Body mass index at the 75th percentile
   d. Polycystic ovarian syndrome

7. Based on data from recent clinical trials, what target hemoglobin concentration for nondialyzed chronic kidney disease patients treated with an erythropoiesis-stimulating agent is associated with the lowest cardiovascular morbidity?
   a. Any hemoglobin concentration is fine; early associations were in error
   b. Target hemoglobin concentrations are the same as those used for patients with chronic kidney disease receiving dialysis
   c. Hemoglobin concentrations should be kept in the normal range (13.0–15.0 g/dL)
   d. Hemoglobin concentrations should be kept between 11.0 and 12.0 g/dL

8. Which of the following factors is most helpful for diagnosing sarcoidosis?
   a. Serum angiotensin-converting enzyme levels of more than twice the upper limit of normal
   b. Histopathological confirmation of noncaseating granulomas
   c. Bronchoalveolar lavage fluid CD4-to-CD8 ratio of more than 3.5
   d. Hilar adenopathy on radiograph