**Evidence-Based Practice** is celebrating 5 years of FPIN member participation, and is proud to be named the official journal of the Family Physicians Inquiries Network.

Many of you have been readers since the debut of EBP in 1998, by Dowden Health Media. FPIN began providing editorial leadership of EBP in 2004. It was in 2005 that the Consortium became the publisher of Evidence-Based Practice, and members began participating in the writing and editing responsibilities. What started as a simple partnership has evolved to a collaborative forum and integrated teaching tool, and is now the official journal of the FPIN Consortium. Thank you for your continued commitment to quality evidence in medicine.

John Saultz, MD
Executive Editor

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**Long-acting β-agonists and inhaled corticosteroids for persistent asthma**

**Bottom line**

For adults with persistent asthma who remain symptomatic while using an inhaled corticosteroid (ICS), the addition of a long-acting β-agonist (LABA) reduces the rate of exacerbations, improves lung function and symptoms, and modestly decreases rescue use of short-acting β₂-agonists. However, risk of death and intubation is slightly increased when LABAs are used with ICSs, compared with inhaled steroids alone.

**Evidence summary**

Salmeterol was the first approved inhaled LABA in 1994. Just 2 years later, the US Food and Drug Administration requested a surveillance study, which showed increased asthma-related deaths, leading to a black box warning for LABA monotherapy in 2005.¹ However, until recently, there has been no indication that the risk of LABAs persists when used with an ICS.

**Evidence of benefit**

A 2010 Cochrane review that included 77 studies concluded that for adults with uncontrolled asthma undergoing ICS monotherapy, adding a LABA decreases the frequency of exacerbations requiring oral steroids, improves lung function, and decreases use of rescue medication. A total of 21,248 patients were enrolled (4,625 children and...
16,623 adults). Participants were generally symptomatic at baseline despite taking an ICS. A LABA, usually formoterol or salmeterol, was added to low-dose ICS (200–400 µg/d beclomethasone or equivalent) in about half of the studies.\(^2\)

With a daily LABA, the risk of exacerbations requiring oral steroids was reduced from 15% to 11% (RR=0.77; 95% CI, 0.68–0.87; in 28 studies with 6,808 participants). The number needed to treat with the addition of LABA to prevent 1 use of rescue corticosteroids was 41. The subgroup estimate for decreased exacerbations in pediatric studies was not significant (RR=0.89; 95% CI, 0.58–1.39).\(^2\)

Among the studies reviewed, the adverse event rate varied from 0% to 38%. The difference in the relative risk of serious adverse events with LABA was not significantly different from that of ICS alone (RR=1.06; 95% CI, 0.87–1.30).\(^2\) It is possible that the studies had too few patients to accurately assess adverse event rates.

### A new meta-analysis with more power

A 2010 meta-analysis evaluated randomized controlled trials of patients with asthma taking LABAs with variable ICS use (<100% of patients) compared with placebo, and concomitant ICS use (100% of patients) compared with ICS alone for the outcome of asthma-related intubation or death.\(^3\) Trials had to have at least 1 asthma-related death to be included.

In pooled trial data that included more than 36,000 participants, LABAs doubled the risk of catastrophic events (Peto OR 2.1; 95% CI, 1.4–3.2). Event risk was significantly increased in trials that used LABAs variably with ICS compared with placebo (OR 1.8; 95% CI, 1.1–2.9) and for concomitant treatment with ICS compared with ICS alone (OR 3.7; 95% CI, 1.4–9.6). When the analysis was restricted to trials with controlled corticosteroid use given as part of the study intervention, combination ICS/LABA treatment still increased catastrophic events compared with ICS alone (OR 8.2; 95% CI, 1.1–61). No significant difference was seen between concomitant and variable ICS use, salmeterol and formoterol use, or children and adults.\(^3\)

### Serious though rare events

The authors did not include 83 trials in this meta-analysis due to lack of serious event reporting. If trials without serious events were also analyzed, there would be 14 adverse events per 35,000 patients treated with combined ICS/LABA (0.04%) as compared with 3 events per 29,000 patients treated with ICS alone (0.01%), or an absolute risk increase of 3 events per 10,000 patients over 5 months and a number needed to harm of 3,333 patients.\(^3\)

Though the authors found a significant increase in risk with combination therapy, the clinical significance of the risk seen here is unclear given the small number of events noted. This small absolute risk increase underscores the need for physicians to discuss benefits and risks with patients. Alternative treatment options should also be reviewed.

Further studies are needed to assess the overall risk-to-benefit profile of LABAs and to investigate possibilities of other agents, such as leukotriene modifiers or anti-IgE therapy, for patients uncontrolled on ICS monotherapy.\(^4,5\)

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**Evidence-Based Practice learning objectives**

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

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**References**


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Evidence-Based Practice

From the Editor

A New Quartet

Dear EBP Readers,

There is something unique about barbershop (or “beauty shop”) quartet music. When the 4 singers hit a dominant 7th chord, they create an overtone that sounds almost like there is a fifth signer in the group. This ringing cord is sometimes even known as the “fifth voice.”

In the upcoming issues of Evidence-Based Practice (EBP), we are going to become something of a quartet ourselves, because we will—for the first time—hear from all 4 academic project arms of the Family Physicians Inquiries Network (FPIN). EBP has historically been something of a soloist as it sheltered, nurtured, and promoted the HelpDesk Answers initiative. But we are not going to be singing solo any more.

Not long ago, when EBP added some Clinical Inquiries (CIs) to our publication, we became a duet. CIs were long the flagship academic project of FPIN. With HDAs doing the melody and a few CIs carrying the deep base notes, EBP was sounding better than ever. So why stop? We decided to add the other 2 voices of FPIN—those of the Priority Updates from the Research Literature (PURLs) group and the eMedRef content.

The PURLs group surveys newly published research trials for important patient-oriented outcomes that have the potential to change practice, if only more family doctors knew about them. “eMedRef” is short for electronic medical reference, which consists of some 2,700 point-of-care topic reviews. The database of these reviews is constantly being updated with information most useful in the clinics, and we think you will want those updates too.

So, as you read the upcoming issues of EBP, please take note of all 4 voices: HDAs, CIs, PURLs, and eMedRef. Somewhere in the mix do you also hear an ethereal “fifth voice”? That, my friend, is the sound of FPIN promoting academic achievement throughout the discipline of family medicine. Sweet!

Regards,

Jon O. Neher, MD

Evidence-Based Practice / Vol. 13, No. 10
Evidence-based answer
In patients without cardiovascular disease (CVD), HMG CoA reductase inhibitor (statin) use safely reduces the 5-year incidence of major coronary events by 29.2%, coronary revascularization by 33.8%, non-fatal myocardial infarction (MI) by 31.7%, and stroke by 14.4%, but with no statistically significant reduction in all-cause mortality (SOR: A, based on an RCT/systematic review). For patients at moderately high risk for CVD, statin therapy is cost effective and reduces major coronary events and CVD (SOR: A, based on an RCT). For patients at low risk, statin therapy is not cost effective.

Evidence summary
CVD is defined as coronary heart disease (CHD), transient ischemic attack and stroke, peripheral vascular disease, or heart failure. Statins decrease low-density lipoprotein-cholesterol (LDL-C) by a mean of 28% and triglycerides by a mean of 20%, and increase high-density lipoprotein-cholesterol by a mean of 5%, inducing clinically important antiatherogenic effects.

Statins lower risk of cardiovascular events, even for patients without CHD
A meta-analysis of 7 RCTs of 42,848 patients, of whom 90% had no history of CVD, demonstrated that statin therapy reduces the relative risk of major coronary events, major cerebrovascular events, and revascularizations by 29.2%, 14.4%, and 33.8%, respectively. Additionally, CHD mortality was reduced 22.6%, but the difference was not significant. The numbers needed to treat to prevent 1 CHD event were 133, 61, and 44 for low-, intermediate-, and high-risk patients, respectively, over an average of 4.3 years.

A meta-analysis of 14 RCTs with 90,056 participants over 5 years revealed statistically significant reductions in MI or coronary death by 23%, coronary revascularization by 24%, fatal or nonfatal stroke by 17%, and major vascular events by 21%. Of those without preexisting CHD, there were 18 fewer participants having major coronary events, 12 fewer participants having stroke, and 25 fewer participants having major vascular events per 1,000 during an average of 5 years.

A Cochrane review (protocol for a systematic review) demonstrated that statin therapy was beneficial in reducing the risk of cardiovascular events. Two subpopulation groups in which statin therapy did not affect CHD mortality were women, and men and women older than 69.

Cost effectiveness of statins varies with patient risk
The meta-analysis of 7 RCTs mentioned above noted that statins are cost effective for primary prevention in high-risk patients who have an absolute 10-year CHD rate higher than 20%. The routine use of statins in the intermediate-risk population (10-year CHD risk, 10%–20%) remains controversial when cost of

### Clinical Inquiries

**ATP III LDL-C goals for drug therapy in different risk categories based on clinical trial evidence**

<table>
<thead>
<tr>
<th>Risk category</th>
<th>LDL-C goal</th>
<th>Consider drug therapy if LDL-C is</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: CHD or CHD equivalent (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL (optional goal: &lt;70 mg/dL)</td>
<td>≥100 mg/dL</td>
</tr>
<tr>
<td>Moderately high risk: 2+ risk factors (10-year risk 10%–20%)</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
</tr>
<tr>
<td>Moderate risk: 2+ risk factors (10-year risk &lt;10%)</td>
<td>&lt;130 mg/dL</td>
<td>≥160 mg/dL</td>
</tr>
<tr>
<td>Lower risk: 0–1 risk factors</td>
<td>&lt;160 mg/dL</td>
<td>≥190 mg/dL</td>
</tr>
</tbody>
</table>

ATP III=Adult Treatment Panel III; CHD=coronary heart disease; LDL-C=low-density lipoprotein-cholesterol.
Evidence-Based Practice / Vol. 13, No. 10

therapy is considered. Statins are not cost effective for primary prevention in low-risk patients (10-year CHD risk, <10%).

The National Institute for Health and Clinical Excellence (NICE) study evaluated the clinical and cost effectiveness of statins for primary prevention of cardiovascular events. This systematic review recommended statin therapy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD.

Recommendations from others

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines recommended an LDL-C target goal of <100 mg/dL in high-risk patients, 130 mg/dL for moderately high and moderate-risk patients, and 160 mg/dL for low-risk patients. For patients with the lowest category risk, NCEP ATP III recommended treatment with a statin for LDL-C ≥190 mg/dL (TABLE 1). In 2004, the guidelines recommended intensification of the LDL-C goal to <70 mg/dL in very high-risk populations.

The European Society of Hypertension recommended an LDL-C target level <77 mg/dL for primary prevention in patients with a 10-year CHD risk greater than 20%.

Cost for statin therapies are provided in TABLE 2.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Bottle contains</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lescol</td>
<td>40 mg</td>
<td>30 capsules</td>
<td>$95.99</td>
</tr>
<tr>
<td>Lescol XL</td>
<td>80 mg</td>
<td>30 tablets</td>
<td>$127.41</td>
</tr>
<tr>
<td>Lipitor</td>
<td>40 mg</td>
<td>30 tablets</td>
<td>$139.99</td>
</tr>
<tr>
<td></td>
<td>80 mg</td>
<td>30 tablets</td>
<td>$139.99</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>40 mg</td>
<td>30 tablets</td>
<td>$35.99</td>
</tr>
<tr>
<td>Pravachol</td>
<td>40 mg</td>
<td>30 tablets</td>
<td>$169.98</td>
</tr>
<tr>
<td></td>
<td>80 mg</td>
<td>30 tablets</td>
<td>$191.66</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20 mg</td>
<td>30 tablets</td>
<td>$27.99</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>80 mg</td>
<td>30 tablets</td>
<td>$32.99</td>
</tr>
</tbody>
</table>

Cost information based on pricing from www.drugstore.com as of September 27, 2010.

References

What blood tests are helpful in diagnosing inflammatory bowel disease?

Evidence-based answer

The typical laboratory tests ordered in a primary care clinic to screen patients for inflammatory bowel disease (IBD) include erythrocyte sedimentation rate (ESR), hemoglobin, platelet count, C-reactive protein (CRP), and albumin levels. These tests are often used as markers of biological inflammation, and are noted to be abnormal in patients with IBD (SOR: B, based on cohort studies). However, they lack specificity for IBD, and currently no published studies have determined the reliability of these tests in clinical practice.

Two newer serological antibody tests, perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA), are highly specific for IBD (SOR: B, based on meta-analyses). Data are inadequate to determine if these tests are appropriate for IBD screening (SOR: C, based on expert opinion).

Evidence summary

Routine screening laboratory tests for IBD typically include ESR, hemoglobin, platelet count, CRP, and albumin levels. Clinical reports suggest these studies are helpful in identifying patients who need further investigation. Some of these tests are sensitive biological markers of inflammation; however, they lack specificity for IBD.1

One study evaluated these tests in a group of pediatric patients referred to a gastroenterology department for further investigation for IBD. The serological tests were performed on all 153 patients who were referred to the clinic. A diagnosis of IBD was then made in 103 of the 153 patients based on the conventional clinical, radiographic, endoscopic, and histological findings.1

The authors concluded that a platelet count of more than 350,000 and anemia (using age-specific criteria) were the best serologic tests differentiating the control group from patients diagnosed with IBD. CRP and albumin did not show evidence of any discriminating power. The authors suggested using a screening strategy of any 2 abnormal results for platelet count, hemoglobin, or ESR to warrant further investigation. This approach had a sensitivity of 85.7% and a specificity of 89.9% based on a prevalence of 67% in the study population.1

A second article looked at these routine blood tests and found that 91% of patients with biopsy-proven IBD had at least 1 abnormal value, compared with 20% of patients in the non-IBD control group.2

Two emerging serologic tests appear to be more specific for IBD, with reported specificities of 92% to 95%.3 Antineutrophil cytoplasmic antibodies with perinuclear highlighting (p-ANCA) has been found to be specific for ulcerative colitis, whereas ASCA has been found to be specific for Crohn’s disease.4

One study performed both p-ANCA and ASCA serologies on the control group and a group of patients already diagnosed with IBD based on conventional clinical, radiographic, endoscopic, and histopathologic findings. The p-ANCA was found to be prevalent in 49.7% of patients with ulcerative colitis, resulting in a specificity of 94%. ASCA was found to be prevalent in 59.7% of patients with Crohn’s disease, resulting in a specificity of 94%.5 These original tests, despite their high specificity, had low sensitivities, ranging from 55% to 70%.3

Previously, the low sensitivities limited their utility as a screening test. However, the tests have recently been modified by recalculating the enzyme-linked immunosorbent assay (ELISA) cutoffs, to increase their sensitivity to 81%, which does lower the specificity to 72%.6 Currently 1 laboratory, Prometheus, offers the “IBD First Step,” which includes the modified serologic tests for both p-ANCA and ASCA.3

Another study evaluated both the modified sensitive ELISA assay and the traditional specific assay on 128 patients who were undergoing diagnostic evaluation for IBD. These authors proposed a new diagnostic testing strategy, whereby sequential confirmatory testing with the traditional assay was performed only in patients who had a positive modified assay result. Patients with a negative assay in either the initial or subsequent assays did not require further evaluation.6

This sequential diagnostic testing reduced the false-positive rate while maximizing the accuracy when compared with performing the modified sensitive ELISA alone. The study reported an overall accuracy of sequential testing to be 84%, with a positive predictive value of 90% and a negative predictive value of 80%.6
A second study evaluated the cost effectiveness of sequential testing and found that there may be up to a 25% reduction in cost if it is used as an alternative to standard endoscopic diagnostic strategies.\(^7\)

**Recommendations from others**

According to the American College of Gastroenterology, the p-ANCA and ASCA assays should not be a first-line screening step or part of the diagnostic workup for IBD at this time because of inadequate data. According to the American College of Gastroenterology’s practice guidelines for ulcerative colitis, the diagnosis is made based on a clinical suspicion with the support of appropriate findings on endoscopic evaluation.\(^8\)

According to the guidelines for Crohn’s disease, the diagnosis is made based on a series of radiologic, endoscopic, and pathologic findings.\(^9\) They stated there may be a role for p-ANCA and ASCA assays in differentiating patients who have IBD into subcategories of Crohn’s disease versus ulcerative colitis. A summary statement noted the current assays are not sufficiently sensitive or specific to be a practical screening tool.

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**REFERENCES**


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**INFLAMMATORY BOWEL DISEASE**

**Two major types**

- Ulcerative colitis
- Crohn’s disease

**Distinguishing the 2 types**

Crohn’s disease can generally be distinguished from ulcerative colitis by the following features of Crohn’s disease:

- Small-bowel involvement
- Rectal sparing
- Absence of rectal bleeding
- Segmental or symmetrical distribution
- Perianal disease
- Associated mass or fistulae
- Patchy lesions or aphthoid, longitudinal, or serpiginous ulcerations at endoscopy
- Transmural disease or granulomas on biopsy

**Ulcerative colitis pearls**

- Treat flare with methylprednisolone, azathioprine, mercaptopurine, and enemas (aspirin, steroid)
- Surgery is curative
- Needs screening colonoscopy every year once a patient has had disease for 8 years

**Crohn’s disease pearls**

- Treat flare with methylprednisolone, azathioprine, mercaptopurine, and metronidazole
- Avoid long-term steroids (they don’t prevent recurrences)
- Extra-articular manifestations: arthritis, sacroiliitis, uveitis, pyoderma gangrenosum, erythema nodosum
- Surgery useful to resect severe inflammation, but disease likely to recur
- Patients with obstructive symptoms may have stricture
eMedRef is FPIN's electronic Medical Reference, and we are excited to share with you portions of these clinical topic reviews as they are completed or updated each month. For more than 5 years, clinicians throughout the FPIN Consortium have worked to develop a comprehensive, high-quality, and easy-to-use point-of-care resource for family physicians and other clinicians who practice in the outpatient, emergency, general inpatient, labor and delivery, or long-term care settings.

We are proud of the more than 2,700 evidence-based clinical topic reviews that have been completed and published. We are also pleased to announce that these will be available for members through the FPIN site search. And while we are proud of our accomplishments, we continue to strive to improve the quality and usability of this resource for all.

Of course, the best way to experience these reviews is in their fully published format supported by the integrated drug database, interactions checker, and calculators. In this format, the Clinical Inquiries, PURLs, and HelpDesk Answers are embedded within each topic. eMedRef reviews are published in PEPID, an online subscription-based publication. To review complete topic monograph visit www.fpin.org/page/ebpemedref.

We hope that you enjoy reading these topics each month, and will engage us often with your questions, comments, and views of these updates. Email us at eMedRef@fpin.org. We want to hear from you!

Brett White, MD
Editor-in-Chief
eMedRef

Syndesmosis: High ankle sprains

Ankle sprain involving 1 or more of the ligaments between the tibia and fibula.
- Commonly underdiagnosed
- Generally seen in football, ice hockey, skiing, and soccer-related injuries

Pathophysiology
- Most common mechanism of injury involves internal rotation of tibia with foot planted
- Incidence ranges from 10% to 20% of all ankle sprains

Therapeutics
Three-Phase Approach
1. Acute protection phase (Days 1–4)
- Non–weight-bearing:
  - Crutches and brace
  - Walking boot, splint, or cast with crutches
- Pain control:
  - NSAIDs
  - Cryotherapy
  - Electrical stimulation
2. Subacute phase (Day 4–5)
- Partial weight-bearing with crutches
- Begin weight-bearing/proprioception exercises to aid in reestablishment of strength/function of basic motions (walking)
- Progress to final phase when able to jog and hop repetitively without difficulty
3. Advanced training phase (Day 6+)
- Full weight-bearing
- More aggressive strengthening, neuromuscular training, and sport-specific exercises

Stability during return to play may be aided by routine ankle taping with additional distal tibiofibular circumferential strips, heel lifts to minimize separation of the distal tibiofibular articulation, and semi-rigid ankle braces.

Prognosis
- Early diagnosis and appropriate treatment essential for a favorable outcome
- Typically has a longer recovery time than other ankle sprains

Author: Hadi Shah, MD, University of Nevada
Editor: Carol Scott, MD, University of Nevada
Hypothyroidism

Therapeutics
Levothyroxine
- Full replacement dose for adult: 1.6 mcg/kg per day
- Usual starting dose for adult < 50 years: 75 mcg/d
- Use lower dose if elderly or heart disease: 12.5–50 mcg/d

Follow-Up
Have patient return to office in 6–8 weeks to check TSH/adjust levothyroxine dose. Once TSH is normal, obtaining annual levels is all that is required. Consider more frequent monitoring if patient is pregnant, using estrogen, has significant weight loss/gain, or return of clinical symptoms. If TSH is not normalizing, consider noncompliance.

Author: Samer Homisha, MD, LSUHSC FMRP Kenner
Editor: Michele McCarthy Larzelere, PhD
LSUHSC FMRP Kenner

Depression in pregnancy
Maternal mental illness can have adverse effects on the cognitive, social, emotional, and behavioral development of infants. Early detection and treatment of depression in pregnancy is critical, as it can adversely affect birth outcomes and neonatal health.

Therapeutics
Cognitive behavioral therapy and interpersonal therapy have been shown to be effective for mild to moderate depression. Pharmacologic therapy is required with more severe presentation, and hospitalization with suicidal or psychotic features.
- All antidepressants cross the placenta and can enter breast milk, but selective serotonin reuptake inhibitors are the mainstay of treatment. Avoid paroxetine (Category D)
- A single medication at a higher dose is preferred over multiple drugs
- See patients weekly until depressive symptoms stabilize
- Drug dose may need to be increased late second trimester, due to decreased serum concentrations during pregnancy

Author: Clara Krebs, MD, Providence/St. Peters FM
Editor: Michele Larzelere, PhD, LSUHSC FMRP Kenner

Polycystic ovarian syndrome

Pears
1. Polycystic ovarian syndrome (PCOS) consists of oligo-ovulation/anovulation together with biochemical hyperandrogenemia and/or clinical hyperandrogenism.
2. The metabolic abnormalities include insulin resistance; untreated PCOS has long-term health risks (diabetes, cardiovascular disease) and immediate issues of menstrual irregularities, hyperandrogenism, and infertility. Endometrial cancer is also a long-term risk.
3. Weight loss and exercise are initial interventions that can effectively address the metabolic abnormalities of PCOS and improve fertility.
4. Treatment needs to be individualized and adjusted for an individual over the course of the reproductive years, from adolescence through menopause.

Recommendations
Based on good and consistent scientific evidence (Level A):
1. Exercise and dietary changes reduce diabetes risk similar to or better than medication.
2. Insulin-sensitizing agents decrease circulating androgen levels, improve ovulation rate, and improve glucose tolerance.
3. Clomiphene citrate is the first-line treatment for ovulation induction.
4. Eflornithine plus laser treatment is superior to laser treatment alone for hirsutism.

Based on limited and inconsistent scientific evidence (Level B):
1. Screen for impaired glucose tolerance and diabetes with a fasting glucose and 2-hour glucose challenge.
2. Screen for cardiovascular risk factors (lipids, BMI).
3. Weight loss can improve pregnancy rates, glucose levels, and lipids, and can decrease hirsutism.

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Joseph B. Stanford, MD, Utah Valley FMR
Editor: Kara Cadwallader, MD, FMR Idaho

We invite your questions and feedback. Email us at EBP@fpin.org.
Use of CT scans for diagnosing appendicitis

Bottom line

The use of preoperative CT scans in the diagnosis of appendicitis has been associated with a significant reduction in the negative appendectomy rate (NAR; the rate of nontherapeutic appendectomy), especially among women of childbearing age. However, for patients with an intermediate probability of appendicitis based on the clinical presentation, a period of observation has good specificity and sensitivity without an increase in complications.

Review of the evidence

Preoperative CT scan reduces needless appendectomies

A 2010 retrospective cohort study compared outcomes in 637 patients who had a CT prior to an appendectomy (between 2003 and 2007) with those among a historical cohort of 971 patients evaluated before the common use of CT in emergency departments (between 1990 and 1994).1

From 1990 to 2007, the NAR decreased significantly from 23.0% (209 of 971 patients) to 1.7% (39 of 637 patients; \( P < .0001 \)). Use of preoperative CT for patients undergoing appendectomy increased from 1% of patients undergoing appendectomy in 1990 to 97.5% of patients undergoing appendectomy in 2007 (\( P < .0001 \)).

In another 2010 retrospective study, researchers reviewed the use of preoperative CT for the evaluation of patients suspected of having appendicitis at 1 institution. The study included 925 patients (57% men and 43% women with a mean age of 38 years) who underwent urgent appendectomy from 1998 to 2007. Pathology reports were used to determine whether or not appendicitis was present.2

Over that time period, the use of preoperative CT increased from 19% to 94% (\( P < .00001 \)). The NAR declined from 17% in 1998 to 9% in 2007 (\( P < .0001 \)). The reduction in the NAR was predominantly seen in females 45 years of age and younger with a change from 43% to 7% (\( P = .0001 \)).

Clinical observation may be OK for intermediate probability of appendicitis

A 2007 prospective randomized trial with 90 women of childbearing age evaluated the role of CT scans compared with continued clinical observation in diagnosing appendicitis. Patients were enrolled if they were thought to have an intermediate probability of appendicitis after clinical and laboratory review by a surgeon.3

No significant difference was noted for sensitivity (observation: 100%, CT: 89.5%; \( P = .21 \)) or specificity (observation: 87.5%, CT: 95.6%; \( P = .61 \)) between the 2 approaches. The likelihood ratio of a positive test (LR+) was 7 for observation and 21 for CT. The negative likelihood ratio was 0.025 for observation and 0.11 for CT.

A 2010 retrospective study reviewed the clinical outcome of 516 patients with CT-diagnosed appendicitis, 13 of whom did not receive immediate therapy based on clinical considerations. Of this latter group, 5 later underwent appendectomy with pathologically proven appendicitis after a mean interval of 118 days.4

The perforation rate in the deferred group (23%; 3 of 13) was higher than in the immediate treatment group (11%; 55 of 499), although this difference was not significant (\( P > .1 \)). This study concluded that for patients with CT results positive for appendicitis and benign or atypical clinical findings, a diagnosis of chronic or recurrent appendicitis may be considered.4

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REFERENCES


Research Family Medicine presented their HDAs during the MO AFP Annual Resident Research Poster Contest, earning 1st, 2nd, and 3rd place. Congratulations Research Family Medicine! To learn more visit: www.fpin.org/page/RFMR
17-alpha hydroxyprogesterone for reducing preterm labor

Bottom line
Supplementation with intramuscular 17-alpha hydroxyprogesterone caproate (17P) significantly reduces the incidence of preterm delivery for women at increased risk of preterm birth. All women with a singleton pregnancy and a history of prior preterm birth should be offered weekly injections. Additional studies are needed to investigate use in women with a short cervix, multiple gestations, and in arrest of preterm labor. Complete maternal and fetal safety profiles, as well as ideal dose, route of administration, and duration of treatment, are also evolving.

Evidence summary
A 2003 trial studied 17P, a natural progesterone metabolite, and its effect on reducing delivery rates before 37 weeks. Multiparous women with a prior preterm delivery were randomized to weekly 17P injections beginning between 15 and 20 weeks and continued until 36 weeks. Ultrasounds were conducted to rule out fetal anomalies and evaluate gestation.\(^1\)

The frequency of delivery before 37 weeks was 36% in the progesterone group, compared with 55% in the placebo group (P<.001; NNT=5). Delivery before 35 and 32 weeks was also significantly decreased in women receiving 17P.\(^1\)

A Cochrane review included 11 RCTs that studied the response of 2,714 women and 3,452 infants to 17P therapy. Benefit was observed for women with a past history of birth before 34 weeks, a short cervix measured on 20-week ultrasound, or multiple pregnancies, and after threatened preterm labor.\(^2\)

A 2008 review of 8 individual RCTs, 6 meta-analyses, and 3 national guidelines supported the use of 17P to reduce the recurrence of preterm births. Some studies specifically evaluated cervical length as measured on ultrasound, and indicated a possible reduction in preterm labor rates in women with a cervical length of <15 mm. Preterm delivery was not significantly reduced among mothers of twins who received 17P. Data on the use of 17P for preterm labor showed overall higher mean gestational age and greater time to delivery. However, sample sizes were small and a lack of blinding affected the strength of these trials.\(^3\)

17P appears to be safe
No current data indicate that 17P therapy is unsafe for women, with the exception of a single retrospective study that found a 13% increase in the incidence of gestational diabetes among women treated with 17P.\(^1\)

Progesterone use contributed significantly to reducing the incidence of low birth weight, necrotizing enterocolitis, supplemental oxygen requirement, and intraventricular hemorrhage in infants. Studies that evaluated the endpoints of perinatal death, respiratory distress syndrome, retinopathy of prematurity, sepsis, and other neonatal comorbidities lacked power.\(^1\) One 4-year follow-up did not identify adverse effects of 17P treatment on children.\(^3\)

Further studies and impact
Although many studies point to the benefits of progesterone therapy, evidence is lacking regarding formulation, dosage, route, and duration of treatment. Additional indications for treatment are also in need of further investigation; as of August 2008, more than 20 progesterone trials for preterm birth prevention were ongoing.\(^3\)

Although 17P may reduce preterm birth rate among women with risk factors, its effect on the national preterm birth rate would likely be modest. Estimates are that use of 17P in women with a prior premature delivery could reduce the US preterm delivery rate from 12.1% to 11.8%, equating to about 10,000 fewer premature births each year.\(^4\)

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REFERENCES
A Tribute

One of the most significant events in the history of the Family Physicians Inquiries Network (FPIN) occurred at the last meeting of the Board of Directors: Bernard Ewigman stepped down as President. This change is significant because the FPIN concept was Bernard's child. Hundreds of people today contribute to FPIN's life and health and growth, but FPIN would not exist at all were it not for Bernard's singular vision and his extraordinary persistence in wrestling this vision into existence.

In 1998, Bernard imagined a world in which family physicians would collectively engage in both asking and answering clinical questions with the best available evidence to solve patient problems, and make those answers immediately available at the point of patient care. He persuaded the American Academy of Family Physicians to award him a grant at the University of Missouri-Columbia, and FPIN was born as 1 of 7 programs in a new family medicine research center.

In 2001, by which time Bernard had persuaded the chairs of 7 of the nation’s leading Departments of Family Medicine to join him, FPIN was officially incorporated, with Bernard as its first and, until our last board meeting, only president. Since its inception, FPIN has undergone enormous change and growth, and Bernard has, with sublime skill, navigated the emerging and changing needs of clinicians and faculty while at the same time holding fast to FPIN's original vision. He has served as the Founding Editor of Clinical Inquiries (2001), Evidence-Based Practice (2004), eMedRef (2004), and the PURLs®—Priority Updates from the Research Literature (2007), of which he is still the Editor in Chief.

Now FPIN has grown up into a life of its own; it is big enough and stable enough to sustain this historic change of leadership. From a seminal concept, FPIN has grown to include more than 140 residency programs, a staff of 10, and several thousand publications that are continuously updated.

Jim Davis, MD, MS, Chair of the Department of Family Medicine at the University of Washington and FPIN Vice President for Finance, has been selected as the new President of FPIN, and will no doubt lead FPIN to even greater success. Bernard will remain on the Board of Directors as the Founding President, a position the board created so as to not lose Bernard’s unmatched leadership and ideas, and in his capacity as Chair of the Departments of Family Medicine at the University of Chicago and at NorthShore University Health System, where every faculty member, fellow, resident, and medical student is actively involved in or touched by FPIN, asking and answering questions with the best available evidence.

Thank you, Bernard, for leading the development of one of family medicine's most valuable organizations.

Frank Verloin deGruy III, MD, MSFM
Chair, Board of Directors, FPIN
Is statin therapy safe and effective for hyperlipidemia in patients with baseline elevated liver function tests or chronic liver disease?

Evidence-Based Answer
Yes. Statins are safe and effective for improving lipid profiles in patients with chronic, stable liver disease, such as nonalcoholic fatty liver disease (NAFLD), steatohepatitis, and compensated cirrhosis with baseline transaminase elevation. In these situations, statins are not associated with any significant increase in transaminases or acute liver injury over placebo. (SOR: B, based on subgroup analysis in a systematic review, an RCT, and cohort studies.)

In a meta-analysis of 3 RCTs, pravastatin 40 mg daily was compared with placebo in more than 19,000 patients. A primary safety outcome was “elevated” alanine aminotransferase (ALT) levels, defined as a value >1.5 times the upper limit of normal (ULN). No statistically significant difference was noted in ALT elevations (8.8% in the pravastatin group vs 8.2% in placebo group; 95% CI for difference, –0.21 to 1.42).1

A subgroup of 579 patients with baseline abnormal ALT levels (1–3 times ULN, representing 3.2% of the pravastatin group and 2.6% of the placebo group) were assessed for exacerbation of underlying liver pathology. During active or placebo therapy, the finding of an ALT level 1.5 to 3 times ULN was comparable (40% [127/317] vs 39% [101/262], respectively; P not reported). There was also no significant difference in the number of patients with baseline elevated ALT experiencing ALT elevations >3 times ULN (5% pravastatin vs 7.3% placebo; P not reported).1

A subsequent double-blind RCT examined the effects of pravastatin 80 mg daily versus placebo in 326 subjects with hyperlipidemia and stable liver disease, including hepatitis C, NAFLD, or elevated aspartate aminotransferase (AST) or ALT up to 5 times ULN. Subjects were studied for 36 weeks with a primary safety endpoint of doubling of elevated baseline ALT.2 The rate of ALT doubling was not statistically significant at any point in the study (7.5% for pravastatin vs 12.5% for placebo at 36 weeks; P=.14). No differences were noted in ALT doubling when patients with normal baseline ALT were examined separately from those with elevated baseline ALT. No subjects experienced acute exacerbation of liver disease.2

A cohort study evaluated 3,399 patients (cohort 1: 135 patients with elevated baseline AST >40 IU/L or ALT >35 IU/L receiving lovastatin; cohort 2: 620 patients with normal enzymes receiving lovastatin; and cohort 3: 2,644 patients with elevated liver enzymes not prescribed lovastatin). Mild-moderate enzyme elevation was defined as ≤10-fold normal and severe elevation >10-fold normal.3 Compared with cohort 2, individuals in cohort 1 had higher incidence of mild-moderate elevations (6.6% vs 3%; P=.03), but not severe elevations (0% vs 0.3%; P=.9). Compared with cohort 3, patients in cohort 1 had similar mild-moderate elevations (6.6% vs 11%; P=.2), but fewer severe elevations (0% vs 5.5%; P<.01).3

Another cohort study with the same inclusion criteria examined 4,024 patients (cohort 1: 342 hyperlipidemic patients with elevated baseline enzymes prescribed atorvastatin, simvastatin, pravastatin, or fluvastatin; cohort 2: 1,437 hyperlipidemic patients with normal enzymes prescribed a statin; and cohort 3: 2,245 patients with elevated enzymes not prescribed a statin.4 Compared with cohort 1, cohort 2 had a lower incidence of mild-moderate elevations (4.7% vs 1.9%; P=.002), but not severe elevations (0.6% vs 0.2%; P=.2). Between cohorts 1 and 3, no differences were noted in mild-moderate elevations (4.7% vs 6.4%, respectively; P=.2) or severe elevations (0.6% vs 0.4%, respectively; P=.6).4

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How safe and effective are platelet-rich plasma injections for decreasing pain in patients with tendinopathy?

Evidence-Based Answer
Platelet-rich plasma (PRP) injections do not result in an increase in infections, hematomas, or tendon ruptures, and are considered safe. (SOR: B, based on 3 prospective trials with 62 total patients.) However, evidence is currently insufficient to recommend PRP injections for patients with tendinopathy pain. (SOR: B, based on a single RCT and 2 cohort studies.)

The term “tendinopathy” describes a chronic tendon overuse injury in the absence of a pathologic diagnosis.\(^1\) Histologic studies have shown that tendinopathy is associated with fibrin deposition, neovascularization, and increased collagen breakdown. This “failed healing response” is thought to be caused by poor blood supply.\(^2\) PRP injections, which contain growth factors and may affect the healing of damaged tissue, have been suggested as a treatment option.

A 2009 stratified, block-randomized, double-blind, placebo-controlled trial evaluated 54 patients with chronic (≥2 months) Achilles tendinopathy. Each patient received either a PRP or saline injection with the aid of ultrasound guidance. All patients completed a detailed rehabilitative program involving a 12-week daily eccentric exercise program. Each patient completed a Victorian Institute of Sports Assessment Achilles (VISA-A) questionnaire at 6, 12, and 24 weeks to quantify pain and activity level. The VISA-A score ranged from 0 to 100. A score of 0 correlates with maximum pain and no activity, while a score of 100 correlates with no pain and maximal activity.\(^3\)

The mean VISA-A score improved significantly after 24 weeks in both the PRP group (+22 points; 95% CI, 13–31) and the placebo group (+21 points; 95% CI, 12–29). No significant difference was noted between the groups in improvement of the VISA-A score. No infections, hematomas, or tendon ruptures occurred.\(^3\)

A 2006 cohort study evaluated patients with chronic elbow tendinosis who failed nonoperative treatment. The study included 20 patients; a single PRP injection was given to 15 patients and a single dose of bupivacaine was given to the other 5. Proper randomization was not followed, no blinding was performed, and 3 of the 5 bupivacaine patients were lost to follow-up. Eight weeks after treatment the PRP group had 60% improvement in a visual analog pain scores versus 16% improvement in the 2 remaining control patients (\(P=.001\)).\(^4\)

A 2008 case series evaluated PRP as treatment for patellar tendinosis. Twenty patients with >3 months of exercise-associated pain were given 3 sets of PRP injections 15 days apart. The primary outcome was change on a 100-point scale of health status at 6 months.\(^5\)

The group’s mean scores improved from about 57 to 82 (\(P<.001\)). Evaluation of functional recovery results showed 6 participants with complete recovery, 8 with marked improvement, 2 with mild improvement, and 4 with no improvement. No infections, hematomas, or tendon ruptures were observed.\(^6\)

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Evidence-Based Answer

No consistent differences have been noted in the cardiac effects of levalbuterol and racemic albuterol when given at equivalent doses and intervals. (SOR: A, based on smaller RCTs.) Both agents are associated with increased cardiovascular events when used in patients with obstructive airway disease. (SOR: A, based on a meta-analysis.)

Levalbuterol (LEV) is purified to contain only the metabolically active R-isomer, whereas racemic albuterol (RAC) is composed of a 1:1 ratio of S- and R-isomers. No clinical trials have demonstrated direct cardiac effects of the S-isomer.

In 2004, a meta-analysis of 33 RCTs (n=6,855) evaluated the cardiovascular effects of beta-2-agonists. The study population had either asthma or chronic obstructive pulmonary disease (COPD). Compared with placebo, beta-2-agonists were associated with a 2.5 relative risk (95% CI, 1.69–4.1) for adverse cardiovascular events (P<.001). While most of these events were sinus tachycardia (RR=3.1; 95% CI, 1.7–5.5), there was a trend for major cardiovascular events, such as heart failure, myocardial infarction, ventricular tachycardia, and death (RR=1.7; 95% CI, 0.76–3.6).¹

One small, prospective, randomized crossover study evaluated the cardiovascular differences between LEV and RAC. The study used 20 ICU patients who were treated every 4 hours with equivalent doses of either LEV or RAC (1.25 vs 2.5 mg, respectively). Both drugs caused a slight increase in heart rate (HR); however, no statistical difference was noted between the 2 medications (3.6 bpm LEV vs 4.4 bpm RAC).²

In a pediatric RCT (n=81), patients with severe asthma exacerbations were given either 10 mg/h of LEV or 20 mg/h of RAC. Tachycardia occurred with a mean HR of 130 to 137 bpm, but no statistically significant difference was noted between the 2 treatment groups.³ In an RCT (n=49) of patients with asthma under good control, researchers found the HR increased by an average of 3.5 bpm more in the RAC vs the LEV treatment group (95% CI, 0.6–6.4).⁴

One large study (n=486) of adults with COPD and asthma exacerbations did show a difference in the subjective sensation of “rapid heartbeat” with RAC (17.3% vs 6.1%; P<.001). No other cardiac data were available from this study. This study used a protocol of RAC every 1 to 4 hours and LEV every 8 hours.⁵

The 2007 National Heart, Lung, and Blood Institute guidelines for asthma exacerbation recommend that the dosing interval for both LEV and RAC is every 1 to 4 hours as needed.⁶

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

What’s in an HDA?

We’ve asked Dr. Robert Gauer, author of numerous HDAs, What goes into writing an HDA?

I generally spend about 3 hours performing a literature search. When I get the articles I want, I go over their bibliographies and pull additional articles, spending about 8–10 hours of reading and processing.

From there, I am able to begin putting thoughts into words. This process takes about 4 hours; then I spend another 2 hours after I’ve let it sit for a few days. After the external peer review and a round or two of edits from Dr. Neher, it is usually ready for print.

My favorite part is the actual writing and seeing how I can take a mountain of information and make it into a molehill that still has relevance for the reader.

I can’t tell you the countless times I have referred to an HDA for a question asked by a student or resident. We find the answer easily, and it takes less than 5 minutes to read.

Read more at: www.fpin.org/page/Gauer

Is acupuncture effective therapy for depression?

Evidence-Based Answer
The answer is unclear. In comparison trials, acupuncture appears to be as effective as antidepressants, but it has not been shown to be better than either sham acupuncture or no active treatment. (SOR: A, based on meta-analysis.) Acupuncture may provide additional improvement in symptoms when used in conjunction with an antidepressant. (SOR: B, based on meta-analysis and RCT with inconsistent findings.)

A recent meta-analysis searched multiple English and Chinese language databases for RCTs that evaluated acupuncture for major depressive disorder (MDD). The investigators ultimately included 20 of the highest quality RCTs. Meta-analysis was performed on 2 outcomes: (1) change in score from baseline on various depression rating scales, and (2) clinical response, defined as a >50% reduction from baseline in depression scores. Most studies used the Hamilton Depression Rating Scale, with scores ranging from 0 to 66, higher scores indicating increased severity of depression.

In the short term (4–12 weeks), acupuncture alone is comparable to antidepressants in clinical response and in decreasing symptom severity (TABLE). When combined with antidepressants, acupuncture is better than antidepressants alone in decreasing symptom severity but not in clinical response.1

Only a few studies of short duration (6–12 weeks) with a small number of patients evaluated acupuncture compared with sham acupuncture or no active treatment; they found no significant differences. No publication bias was noted, but the studies were heterogeneous, differing in acupuncture technique, number of treatment sessions, and treatment duration.1

A subsequent RCT (n=80) evaluated the combination of acupuncture and low-dose fluoxetine for depression. Patients with MDD were randomly allocated to either acupuncture and fluoxetine 10 mg/d (ACP group) or sham acupuncture and fluoxetine 20 mg/d for 2 weeks, then 30 mg/d (SACP group). Patient and outcome assessors were blinded to treatment assignment.2

After 6 weeks, intention-to-treat analysis of clinical response rates (again defined as >50% decrease from baseline score on the Hamilton Depression Rating Scale) were similar in both groups (80% in the ACP group and 78% in the SACP group, P=.79). However, the authors reported the ACP group had significantly lower scores on the Åsberg Rating Scale for Side Effects, presumably secondary to lower doses of fluoxetine.2 Mean scores were not numerically reported, which makes determination of clinical significance difficult.

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<table>
<thead>
<tr>
<th>Intervention and control groups</th>
<th>Outcome</th>
<th>Number of studies</th>
<th>Number of patients</th>
<th>Pooled results</th>
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<tr>
<td>ACP vs AD</td>
<td>CR</td>
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<td>1,030</td>
<td>RR=1.06 (95% CI, 0.97 to 1.17; P=.20)</td>
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<td>DS</td>
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<td>ACP + AD vs AD</td>
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<td>DS</td>
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<td>109</td>
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<td>ACP vs sham ACP</td>
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<td>RR=1.27 (95% CI, 0.58 to 2.80; P=.55)</td>
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ACP=acupuncture; AD=antidepressants; CR=clinical response; DS=decreasing symptom severity; NA=not available; RR=relative risk; WMD=weighted mean difference.

What are the risks of using atenolol for blood pressure control during pregnancy?

Evidence-Based Answer

When compared with other blood pressure (BP) medications or placebo, atenolol use during pregnancy has adverse effects on fetal growth, which increase with the duration of treatment. (SOR: A, based consistent RCTs and cohort studies.)

A prospective, double-blind RCT enrolled 33 women with mild chronic hypertension. Patients were recruited between 12 and 24 weeks’ gestation. Fifteen women received 50 mg atenolol daily, increasing until either BP was less than 140/90 mmHg or a dose of 200 mg was reached. The rest received placebo. No additional drugs were used by the women.

Mean BP after entry to the study was 132/74 mmHg in the atenolol group, and 136/81 mmHg in the placebo group. Babies in the atenolol group had a significantly lower birth weight than those in the placebo group (2,620 vs 3,530 g, respectively; 95% CI for difference, 440–1,380 g; P<.001). The study concluded that atenolol given from the end of first trimester in patients with mild chronic hypertension is associated with intraterine growth restriction.

In a second double-blind RCT, women at risk of developing preeclampsia were given 100 mg atenolol or placebo. A total of 68 patients were recruited between 22 and 25 weeks’ gestation; 48 were nulliparous and 20 had diabetes. Among the nulliparous women, treatment with atenolol was associated with infants weighing an average of 440 g less than infants in the placebo group (P=.02). No effect on birth weight was seen in the patients with diabetes.

These findings are similar to those of a retrospective cohort study of 312 pregnancies in 223 hypertensive women attending an antenatal hypertension clinic. Atenolol as monotherapy was given in 78 pregnancies (25%); other antihypertensive agents were given as monotherapy in 53 pregnancies (17%); multiple drug combinations were given in 90 pregnancies (29%); and no antihypertensive agents were given in 91 pregnancies (29%).

When atenolol monotherapy was compared with other antihypertensive drugs as monotherapy or with no treatment, atenolol was found to be associated with lower mean birth weight (2,372 vs 2,756 vs 3,068 g, respectively; ANOVA P<.05), higher prevalence of preterm (<37 weeks) delivery (33% vs 26% vs 15%; P<.001), and small-for-gestational age (SGA) babies (49% vs 34% vs 21%; P<.001). Women who received atenolol in early pregnancy (<20 weeks) had babies with a significantly lower mean birth weight when compared with mothers started on atenolol at a later stage of pregnancy (>30 weeks) (2,010 vs 2,644 g; P<.05). There was also a significantly higher proportion of SGA babies in the group with early onset of treatment compared with a later start (70% vs 39%; P=.01). Three stillbirths occurred in women with early onset of treatment.

The Society of Obstetricians and Gynaecologists of Canada’s systematic review of the treatment of hypertensive disorders of pregnancy recommends against the use of atenolol. The guideline states that atenolol may be associated with adverse effects on fetal growth. Therefore, other agents are preferable.

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Evidence You Can Trust

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In a patient with panic disorder, is therapy, medication, or both better for long-term treatment and prevention of symptoms?

Evidence-Based Answer

In the first 6 months or so, psychotherapy or antidepressant monotherapy are each about as effective as combined therapy (psychotherapy and an antidepressant) for treating panic symptoms. However, 6 to 24 months after treatment discontinuation, patients who received psychotherapy early on had fewer relapses. (SOR: A, based on a systematic review.) Adding a benzodiazepine to psychotherapy does not improve its effectiveness or alter the long-term relapse rate. (SOR: A, based on a systematic review.)

A Cochrane review compared combined treatment with psychotherapy (primarily behavior and cognitive-behavioral therapy) and an antidepressant (primarily tricyclic antidepressants or selective serotonin reuptake inhibitors) to psychotherapy or an antidepressant alone in adult patients with panic disorder, with or without agoraphobia. Outcomes were assessed after both long-term treatment (with a 2- to 4-month acute treatment phase, followed by a 12- to 36-week continuation phase [5 trials, n=382]) and 6 to 24 months after treatment discontinuation (5 trials, n=376). Antidepressants were continued throughout the treatment phase, and psychotherapy was provided during the acute phase and occasionally longer.

The response/remission rate during long-term treatment for those who had received combined therapy was not superior to those who received antidepressants alone (RR=1.3; 95% CI, 0.75–2.4; P=.32). However, the response/remission rate of those who had received combined therapy was superior to antidepressants at 6 to 24 months after treatment discontinuation (RR=1.6; 95% CI, 1.2–2.1; P<.001). Dropouts were not different between treatment arms for long-term treatment (RR=0.7; 95% CI, 0.3–1.9; P=.50).

In 3 of the studies (n=229), combined therapy was not superior to psychotherapy alone for long-term treatment (RR of response/remission=1.3; 95% CI, 0.93–1.7; P=.14). At 6 to 24 months after treatment discontinuation (8 trials, n=507), no advantage of combined therapy over psychotherapy was observed (RR=0.93; 95% CI, 0.76–1.2; P=.52). No difference was noted in dropout rates for any reason between combined therapy and psychotherapy (2 trials, n=147) during long-term treatment (RR=0.78; 95% CI, 0.25–2.4; P=.67). Similar effectiveness for patients with and without agoraphobia was reported in a subgroup analysis.1

A meta-analysis compared combined treatment with both psychotherapy and a benzodiazepine to either psychotherapy or a benzodiazepine alone for long-term treatment of adults for panic symptoms.2

Two trials (n=166) compared psychotherapy plus a benzodiazepine (alprazolam or diazepam) vs psychotherapy. Combined therapy was not superior to psychotherapy after 16 weeks of treatment (RR=0.78; 95% CI, 0.45–1.4; P=.37) or 7 to 12 months after all interventions had ended (RR=0.62; 95% CI 0.36–1.1; P=.08). The combination and psychotherapy groups had similar dropout rates (RR=0.91; 95% CI, 0.57–1.5; P=.71).

For combination therapy vs a benzodiazepine alone, only 1 trial (n=77) met inclusion criteria. Psychotherapy plus a benzodiazepine was modestly superior to a benzodiazepine alone at the end of 16 weeks in pooled outcome measures (RR=3.4; 95% CI, 1.0–11; P=.05). However, 7 months after all treatments had ended, outcomes were similar (RR=2.31; 95% CI, 0.79–6.7; P=.12).

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FPIN Podcasts

Connie Kraus, PharmD, and the University of Wisconsin are long-time members of the FPIN Consortium and regular contributors to Evidence-Based Practice.

To learn more about how Dr. Kraus has integrated the principles of evidence-based medicine into her students’ curriculum, download her podcast at www.fpin.org/page/podcasts.
Risks and benefits of creatine supplementation

Bottom line
Creatine supplementation increases muscle power output in as little as 1 week. (SOR: A, based on consistent RCTs.) Even patients with hereditary muscular dystrophies experience increased muscle strength. (SOR: A, based on a systematic review.) Creatine appears to elevate serum creatine kinase activity, but the clinical significance of this effect is unclear. (SOR: C, based on bench research with limited numbers of patients.) Dose-dependent diarrhea is the most notable side effect. (SOR: B, based on a single RCT.)

Evidence summary
A 4-week RCT conducted in 2009 that included 42 active college-aged men showed that critical muscle power—the maximum power output that can be obtained without fatigue—increased 6.7% in subjects taking creatine supplementation (P=.013).1 A 2005 RCT included 23 young men who performed a series of 5 Wingate tests (30-second bursts of cycling with resistance) before and after 7 days of creatine supplementation. Subjects who consumed the creatine supplementation showed a 7.6% increase in total power output averaged over the 5 tests (P<.01).2

A 2006 meta-analysis of 12 RCTs of creatine treatment (n=266) showed an increase in muscle strength for those with muscular dystrophies. Maximum voluntary contraction in the creatine group improved compared with placebo, with a weighted mean difference of 8.5% (95% CI, 3.6–13). None of the trials reported any clinically relevant adverse events.3

A 2007 RCT determined the effects of creatine supplementation on kidney function in 18 sedentary but healthy males who started a training program and were followed for 3 months. No significant difference was noted between baseline and postexercise program electrolyte levels in either group. Cystatin C (an estimate of glomerular filtration rate) was decreased in both groups, indicating a benefit from exercise rather than creatine supplementation.4

Another 2007 RCT collected renal, hepatic, metabolic, and muscular function markers in 14 football players before and after 8 weeks of creatine supplementation while undergoing sport-specific training. Neither group showed any significant differences in any of the urine tests, but creatine supplementation significantly lowered serum glucose (from 94.9 to 83.0 mg/dL; P=.01), and raised creatine kinase (from 8.0 to 8.6 IU/L; P=.04).5

A 2008 RCT compared 5 g creatine twice daily (n=21) and 10 g creatine once daily (n=18) with placebo (n=20) to assess gastrointestinal (GI) symptoms of creatine supplementation over 4 weeks. No significant differences were noted between the 5-g twice daily and placebo groups. The 10-g once daily group experienced a significant increase in self-reported diarrhea over the placebo group (55.6% vs 35.0%; P<.05). These results suggest that taking 10 g creatine per day does not increase adverse GI symptoms as long as it is divided into at least 2 doses.6

REFERENCES
What is the most effective method for screening for depression in the nursing home setting?

Bottom line
The Geriatric Depression Scale (GDS) is a valid and reliable depression screening instrument, and it performs better than other validated tests among institutionalized elderly patients without cognitive impairment. (SOR: A, based on validating cohort studies.)

Evidence summary
GDS is the most sensitive scale for nursing home patients
A study published in 2004 assessed the validity of various depression scales for patients in clinics (n=125), hospitals (n=150), and nursing homes (n=85). All patients were assessed using the Yale 1-question screen, the 2-question instrument derived from the Primary Care Evaluation of Mental Disorders, the long and short versions of the Center for Epidemiologic Studies Depression (CES-D) scale, and the GDS. Sensitivity and specificity were calculated for each instrument compared with the criterion-standard Diagnostic Interview Schedule depression diagnosis.1

The GDS was found to be the most appropriate for the nursing home setting (sensitivity 86%, specificity 82%), whereas the short version of the CES-D was most suitable for the clinical (sensitivity 79%, specificity 81%) and hospital (sensitivity 92%, specificity 77%) settings. The CES-D had a lower combined sensitivity (71%) and specificity (83%–85%) than the GDS in the nursing home population.1

Screen for depression with either the CSDD or GDS-15
A 2008 study used observer-rated (Cornell Scale for Depression in Dementia; CSDD) and self-rated (15-item Geriatric Depression Scale, GDS-15) depression rating scales to identify cases of depression in residents living in aged care facilities, including both high care (nursing home level) and low care (assisted living). In addition, a sample of subjects (n=31) were assessed clinically and, where appropriate, diagnosed by a psychiatrist.2

Psychiatric assessment showed that the CSDD ratings identified far more subjects to be depressed (n=17) than the proportion found to fulfill criteria for a DSM-IV depressive disorder (sensitivity 80%, specificity 50%). The GDS-15, on the other hand, correlated well in relation to subjects diagnosed with depression (n=7) by the psychiatrist (sensitivity 60%, specificity 85%). The authors recommended screening for depression with either the CSDD or GDS-15 (in those without severe cognitive impairment) to identify residents who should receive intervention for depression.2

MADRS detects small changes in severity of depression
Another 2008 study evaluated the 30-, 15-, and 8-item versions of the GDS for screening and assessing changes in severity of depression in nursing home patients (n=350) compared with the Montgomery-Åsberg Depression Rating Scale (MADRS). The internal consistency of the 3 GDS versions and the MADRS was good (Cronbach alpha 0.88 for GDS-30, 0.79 for GDS-15, 0.80 for GDS-8, and 0.85 for MADRS). The receiver operator characteristic curves showed the 3 GDS versions would perform well in screening for depression.3

The effect size was larger for the MADRS, indicating better performance measuring changes in severity of depression. However, the GDS was noted to be easier and less time-consuming to administer, which might outweigh the performance benefits of the MADRS in practice.3

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REFERENCES
The course of bipolar disorder is generally chronic and involves 1 or more episodes of mania or mixed mood. Bipolar disorder may also involve depressive episodes, psychotic features, or both. A purely manic episode is characterized by an excessively euphoric or irritable mood, accompanied by other symptoms that may include grandiosity, pressured speech, flight of ideas, distractibility, agitation, risky behavior, and a decreased need for sleep. Manic episodes typically have a sudden onset and can persist for several months. A depressive episode is characterized by a loss of interest or pleasure in nearly all activities. Individuals experiencing a mixed mood episode have a combination of symptoms. The prevalence of bipolar disorder is 0.4% to 1.6% in community samples; the average age of onset is 20 years.

In general, atypical antipsychotics produce antipsychotic responses with fewer acute extrapyramidal adverse effects than “conventional” antipsychotic drugs. Extrapyramidal adverse effects are a set of movement disorders such as akathisia, dystonia, and pseudoparkinsonism that resolve when the drug is discontinued or the dosage is lowered. Tardive dyskinesia is a movement disorder that can develop with more prolonged use and may persist even after cessation of the antipsychotic agent. Atypical antipsychotics are associated with lower rates of the development of this neurological adverse effect in comparison with the older, conventional agents. Atypical antipsychotics may also treat negative symptoms and improve cognitive functioning.

In adults with bipolar disorder, no significant differences were found between risperidone and olanzapine or asenapine and olanzapine in quality of life, remission, and response outcomes. Olanzapine resulted in greater mean weight gain compared with asenapine and risperidone, respectively, whereas asenapine resulted in a significantly higher rate of discontinuations due to adverse events than olanzapine.

In children and adolescents with bipolar disorder evidence is extremely limited; olanzapine and risperidone had similar response rates after 8 weeks of treatment, and no significant differences in mean weight gain were found.

The Drug Effectiveness Review Project (DERP) is a collaboration of organizations that have joined together to obtain the best available evidence on effectiveness and safety comparisons between drugs, and to apply the information to public policy and decision making in local settings. For more information on the organization, visit: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/index.cfm
Are cannabinoids safe and effective for treatment of patients with rheumatoid arthritis?

Bottom line
Sativex® (an oral-mucosal cannabinoid spray containing tetrahydrocannabinol and cannabidiol), as an adjuvant treatment, improves morning pain with movement and at rest, and sleep quality, with minimal adverse events, for patients with rheumatoid arthritis (RA) refractory to standard therapy. Morning stiffness was not significantly improved. (SOR: B, based on a single small RCT.) Sativex is not yet available in the United States.

Evidence summary
A multicenter, randomized, double-blind, parallel-group comparison trial (total n=58; treatment group=31; control group=27) compared Sativex with placebo for ancillary treatment of RA over a total of 5 weeks, including an initial 2-week titration period. A key inclusion criterion was prior failure to achieve adequate pain control using standard treatment for RA (nonsteroidal anti-inflammatory drugs, prednisolone, and/or disease-modifying antirheumatic drugs). Patients with a history of substance abuse; psychiatric conditions; cardiac, hepatic, or renal disorders; or a diagnosis of epilepsy were excluded.¹

The primary outcome measure was pain on movement (measured each morning with numerical rating scale of 0–10). Secondary measures (mostly measured on scales of 0–10, with 10 being the most severe pain) included such outcomes as pain at rest, morning stiffness, and sleep quality.¹

Patients began with a dose of 1 actuation (containing 2.7 mg tetrahydrocannabinol and 2.5 mg cannabidiol in the treatment group) 30 minutes before bedtime. Bedtime dosing was used to reduce symptoms of intoxication. Both Sativex and placebo were titrated by 1 actuation every 2 days up to a maximum daily dose of 6 actuations. Patients continued their standard therapy throughout the trial.¹

Statistical significance was achieved for the primary outcome, decreased pain on movement (mean difference –0.95; 95% CI, –1.83 to –0.02; P= .044).¹ Two secondary measures also improved significantly: pain at rest (mean difference –1.04; 95% CI, –1.90 to –0.18; P=.018) and sleep quality (mean difference –1.17; 95% CI, –2.20 to –0.14; P=.027). Changes in morning stiffness did not reach statistical significance.

Most adverse events were reported as mild to moderate. Constipation and malaise were occasionally severe, but occurred more often in subjects using placebo (6 of 27 patients) than in those using Sativex (2 of 31 patients; no P value reported for comparison). Mild transient dizziness was reported by 8 of 27 patients in the Sativex group and 1 of 31 patients in the placebo group (no P value reported). One subject withdrew from the Sativex group because of a need for surgery (not related to the protocol), whereas 3 in the placebo group dropped out because of adverse events.¹

Product information
Sativex is not currently available in the United States.² GW Pharmaceuticals and their American licensing partner, Otsuka Pharmaceutical Company Ltd, have recently completed Phase IIb trials of Sativex in patients with cancer pain and have applied to the FDA to start Phase III for that indication.

Sativex has been approved for use with cancer pain and multiple sclerosis spasticity in Canada and is currently undergoing regulatory examination for these indications in the United Kingdom and Spain.

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REFERENCES

1. For what patient population is the use of abdominal CT scans most helpful in reducing the negative appendectomy rate?
   - a. Men >65 years old
   - b. Women >65 years old
   - c. Men <45 years old
   - d. Women <45 years old

2. Which of the following statements is true regarding 17-alpha hydroxyprogesterone?
   - a. It is only available as a vaginal suppository
   - b. It is contraindicated in women with a short cervix
   - c. It reduces the preterm delivery rate of women with a prior preterm delivery
   - d. It has been correlated with an increased rate of fetal intraventricular hemorrhage

3. Which of the following statements is true about the use of atenolol in pregnancy?
   - a. Atenolol appears to be more of a problem later in pregnancy
   - b. The risk of low birth weight increases with the duration of atenolol therapy in pregnancy
   - c. Atenolol can be used as safely as other antihypertensive drugs to control blood pressure during pregnancy
   - d. None of the above

4. Currently, platelet-rich plasma injections:
   - a. Have been studied in >1,000 patients
   - b. Generally appear to be safe
   - c. Have not been studied in any randomized controlled trials
   - d. Are underutilized in primary care

5. Which statement is true about the use of diuretics to treat lymphedema?
   - a. Loop diuretics are first-line therapy
   - b. Diuretics have been thoroughly studied and are efficacious
   - c. Chlorothiazide is the only diuretic that has been studied
   - d. None of the above

6. Using the glycosylated hemoglobin (HbA1c) value for diagnosing diabetes, it is important to remember
   - a. The test will miss about 37% of cases using a cutoff of 6.1%
   - b. Values <6.0% are not associated with an elevated risk of diabetes
   - c. The HbA1c level is more accurate than the old oral glucose tolerance test
   - d. A value of 6.2% is 1 standard deviation above the normal level

7. Which electrolyte abnormality is associated with creatine supplementation?
   - a. Hypokalemia
   - b. Hyperkalemia
   - c. Hypernatremia
   - d. None of the above

8. The Geriatric Depression Scale:
   - a. Is specifically designed for use in patients with severe cognitive impairment
   - b. Has a greater sensitivity than the Center for Epidemiologic Studies Depression (CES-D) scale in the nursing home setting
   - c. Is better than the Montgomery-Åsberg Depression Rating Scale (MADRS) for detecting small changes in the severity of depression
   - d. Is a 20-question instrument given by a trained interviewer

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The Department of Family Medicine at the University of Colorado Denver Health Sciences Center is seeking a full-time ABFM-certified or eligible family physician for our community-based program. The Rose Residency is located at Rose Medical Center, ranked nationally as a top 100 hospital, and is supported by the Colorado Health Foundation, a nonprofit organization dedicated to making Colorado the healthiest state in the nation. Applicants must possess or be eligible for medical licensure in the State of Colorado. Applicants must demonstrate experience and competence in teaching and patient care. This is a full-time position with obstetric skills and hospital call required. Women and minorities encouraged to apply. Detailed job descriptions and qualifications required can be found on jobsatcu.com and the Department’s website, http://fammed.ucdenver.edu/home/careers.aspx.

Job Responsibilities: Applicant will be a core member of the Residency Teaching Faculty: Teaches residents, supervises residents and students in the provision of patient care, provides direct patient care in the inpatient and outpatient setting, participates in scholarly activity, and serves as a leader and role model for residents.

Required Qualifications: MD/DO degree, Colorado Medical License, DEA Certificate, Board Certified/Board Eligible in Family Medicine. Practices full spectrum of Family Medicine, including obstetrics and inpatient medicine. Must obtain medical staff privileges within the HealthONE LLC d/b/a/ Rose Medical Center and obtain medical staff privileges at University of Colorado Hospital.

Preferred Qualifications: Experience in family medicine teaching/practice preferred.

Salary is commensurate with skills and experience. Information on University benefits programs, including eligibility, is located at http://www.cu.edu/pbs/.

Applications are accepted electronically at www.jobsatcu.com.

Review of applications will begin February 16, 2010, and continue until position is filled.

When applying at www.jobsatcu.com, applicants must include:
1) A letter of application which specifically addresses the job requirements and outlines qualifications.
2) A current Curriculum Vitae.

Questions should be directed to regina.garrison@ucdenver.edu.

The University of Colorado Denver and Health Sciences Center requires background investigations for employment.

The University of Colorado is committed to diversity and equality in education and employment.

Oregon Health Science University, Department of Family Medicine is seeking family medicine physicians. Responsibilities include providing direct patient care for a panel of patients, precepting residents, and students in a model ambulatory practice and supervising residents on an inpatient teaching service. Inpatient service and obstetrical care are strongly preferred, but not required. Evenings and Saturdays on rotation are required; preference will be given to individuals with greater weekend and evening availability. Practice with a talented dynamic group of colleagues and enjoy the support of a well-integrated medical staff. Qualifications include completion of professional training to receive either the MD or DO degree, as well as graduate medical education in an ACGME-accredited family medicine residency. Board certification or board eligibility required, as well as unrestricted medical license and hospital credentialing. www.ohsu.edu/family-medicine

Send resume with three references to:
Laurie Charron, Mail Code FM
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Portland, OR 97239
charronl@ohsu.edu

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The University of Colorado Family Medicine Residency seeks a full-time faculty member to teach and practice the full scope of family medicine in our innovative P4 family medicine residency. We are committed to training physicians equipped to practice comprehensive primary care with grounding in patient-centered medical home concepts. The successful candidate will be responsible for supervising residents & students in the outpatient and inpatient settings, including obstetrical care, curricular design and teaching, advising residents, and direct patient care at the A. F. Williams Clinic.

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