Treatment of menopausal symptoms

Evidence-based answer

Hormone therapy is the most effective treatment for postmenopausal symptoms (SOR: A, based on a systematic review). For vasomotor symptoms, a variety of nonhormonal prescription therapies have proven efficacy; these include clonidine, gabapentin, selective norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs) (SOR: B, based on a systematic review and RCTs).

Evidence summary

Vasomotor instability, night sweats, and vulvovaginal symptoms are among the most common complaints during the menopausal transition. They occur in more than 70% of postmenopausal women in the United States between the ages of 50 and 79.\(^1\)

HT alleviates vasomotor symptoms

A Cochrane meta-analysis of 24 double-blind RCTs (n=3,229) investigated the effectiveness of estrogen or estrogen/progesterone hormone therapy (HT) for vasomotor instability in menopausal women. The age range of participants was 34 to 64 (mean, 50 years) and study trials ranged from 3 to 36 months in duration. Women using HT had a mean reduction of approximately 18 hot flushes per week compared with placebo (weighted mean difference [WMD] \(-18\); 95% CI, \(-23\) to \(-13\)). This was equivalent to a 75% reduction in frequency (95% CI, 64–82) for HT relative to placebo. The authors concluded oral HT was highly effective in alleviating vasomotor symptoms, but was associated with an increased occurrence for any adverse event (OR 1.4; 95% CI, 1.00–1.99, \(P=.05\)).\(^1\)

HT aids in urogenital atrophy

A Cochrane meta-analysis of 19 RCTs of menopausal women (n=4,162) with urogenital atrophy found estrogen to be more effective than nonhormonal lubricants or placebo for menopausal vaginal symptoms.\(^2\) Estrogen tablets versus placebos showed a significant improvement in vaginal burning and itching (OR 0.15; 95% CI, 0.10–0.20) and dyspareunia (OR 0.17; 95% CI, 0.12–0.23). Dryness was reported less frequently with vaginal tablets compared with placebo (OR 0.08; 95% CI, 0.06–0.10). Vaginal estrogen was superior to lubricants for
In Depth

Nonhormonal intervention for hot flushes in women with a history of breast cancer

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n</th>
<th>Daily dose (oral)</th>
<th>Duration (weeks)</th>
<th>Absolute change in hot flush frequency vs placebo ($P$)</th>
<th>Absolute change in hot flush severity vs placebo ($P$)</th>
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<tbody>
<tr>
<td>Gabapentin</td>
<td>347</td>
<td>900 mg</td>
<td>8</td>
<td>−29% (.001)</td>
<td>−31% (.007)</td>
</tr>
<tr>
<td>(Pandya 2005)*</td>
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<tr>
<td>Clonidine</td>
<td>194</td>
<td>0.1 mg</td>
<td>8</td>
<td>−14% (.006)</td>
<td>−19% (.006)</td>
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<td>(Pandya 2000)*</td>
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<tr>
<td>Vitamin E</td>
<td>105</td>
<td>800 IU</td>
<td>4</td>
<td>−3% (.9)</td>
<td>−3% (≤.5)</td>
</tr>
<tr>
<td>(Barton 1998)*</td>
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<tr>
<td>Fluoxetine</td>
<td>68</td>
<td>20 mg</td>
<td>8</td>
<td>−19% (.01)</td>
<td>−24% (.02)</td>
</tr>
<tr>
<td>(Loprinzi 2002)*</td>
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<tr>
<td>Paroxetine</td>
<td>107</td>
<td>20 mg</td>
<td>8</td>
<td>−25.1% (.002)</td>
<td>−26.9% (.001)</td>
</tr>
<tr>
<td>(Stearns 2005)*</td>
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<tr>
<td>Venlafaxine</td>
<td>191</td>
<td>37.5 mg 75 mg 150 mg</td>
<td>4</td>
<td>−11% (.001)</td>
<td>−34% (.001)</td>
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<td>(Loprinzi 2000)*</td>
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</tbody>
</table>


TABLE

improving vaginal dryness (WMD 4.5; 95% CI, 0.76–6.2) and moisture (WMD 1.04; 95% CI, 0.77–1.3) according to a vaginal health index score.

Nonhormonal remedies also lessen hot flushes

A meta-analysis of 10 RCTs of women with a history of breast cancer demonstrated that several nonhormonal prescription therapies are effective in improving hot flushes. The number of participants per study ranged from 15 to 420 (mean, 85). Primary outcomes reported were frequency and severity of hot flushes (numeric measure 1–4) over a span of 4 to 12 weeks.

Clonidine, gabapentin, SNRIs, and SSRIs reduced both the number and severity of hot flushes. A study using sertraline (50 mg daily) did not show a statistically significant difference for complete resolution of hot flushes at 6 weeks compared with placebo. However, in the crossover design, subjects changing from placebo to sertraline had a 0.9-event decrease in daily hot flushes compared with a 1.5-event increase changing from sertraline to placebo ($P$=.03). Vitamin E was not effective in reducing hot flush symptoms (TABLE).

Recommendations

The Women’s Health Initiative published evidence of increased risks of myocardial infarction, stroke, invasive breast cancer, and thromboembolic events in postmenopausal women treated with HT. In light of these findings, the US Preventive Services Task Force recommended against the routine use of HT for the prevention of chronic conditions in postmenopausal women.

The North American Menopause Society (NAMS) and the American College of Obstetricians and Gynecologists (ACOG) issued statements supporting HT for the treatment of moderate to severe menopausal symptoms. ACOG recommends that HT be limited to the lowest effective dose and shortest time necessary to treat symptoms. HT is the only FDA-approved treatment for hot flushes; however, both NAMS and ACOG recognize nonhormonal therapies as an acceptable alternative in women who wish to avoid estrogens or have a contraindication.

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The opinions and assertions contained herein are the private views of the author 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.

REFERENCES

From the Editor

Dear EBP Readers,

Social networking sites have recently helped coordinate a vast outpouring of political energy in North Africa and the Middle East. Crowds took to the streets, “presidents for life” trembled (or got violent), and change was in the air. Throughout the region, it was evident that the tools of the digital age had greatly empowered many otherwise voiceless individuals.

But digital empowerment is not limited to political groups in faraway autocracies. Social networking has started to shape our very own primary care clinic experience. One laudable aspect of the Web is that people can independently learn about their health and illnesses. One bad part about the Web is that it can spread some tenuous medical ideas around pretty darn fast, particularly through those same social networking sites that are now plaguing two-penny desots.

A recent issue of Scientific American discussed what happened when Paulo Zamboni published an article describing a positive effect from cervical venous dilation in patients with multiple sclerosis.1 This was essentially a case series; no one claimed it was definitive evidence. But soon after the article appeared, the information “went viral” through social networking sites, and vascular surgeons far and wide were suddenly being asked to perform venous dilation by desperate people with multiple sclerosis.

Never mind that there was no placebo group, that follow-up was only 18 months, and that this is an extremely fickle disease. Never mind that venous dilation may need to be repeated multiple times or cost thousands of dollars. Ill people have always been anxious to get better; but now they can communicate faster, sometimes, than the pace of reflection.

Fortunately, the National MS Society is putting together a rigorous study to test the venous dilation hypothesis, although the results will not be available for a few years. In the meantime, physicians must be prepared to help the public interpret this and other medical information circulating on the Web’s social networking sites.

Digital communication may have snuck up on the tyrants. But we hope that your affiliation with this journal and FPIN is helping you develop the necessary skills to meet this modern challenge in the office.

Regards,

Jon O. Neher, MD

REFERENCE

Levonorgestrel intrauterine system reduces menorrhagia


This RCT enrolled 165 parous women with heavy menstrual bleeding to receive either a levonorgestrel-releasing intrauterine system (LNG-IUS) or oral medroxyprogesterone acetate (OMA) 10 mg for 10 days starting on cycle day 16. The primary outcome studied was menstrual blood loss during 6 cycles.

The LNG-IUS group had a mean decrease in menstrual blood loss from baseline of –70.8 mL (SD 88.3), the OMA a mean decrease from baseline of –21 mL (SD 35). Both treatments were well tolerated.

Bottom line: LNG-IUS is already being used in practice to decrease heavy menstrual bleeding, so even if the study had shown clinically meaningful outcomes (which it did not), these findings would not lead us to a change in practice.

An antibiotic provides short-term relief in IBS


This RCT studied the nonabsorbed antibiotic rifaximin for treatment of irritable bowel syndrome (IBS). Patients meeting Rome II criteria for IBS received either a single 2-week course of rifaximin 550 mg 3 times a day (625 patients total among 2 identical, parallel arms) or placebo (635 patients total) and were followed for 12 weeks.

Of patients receiving rifaximin, 40.7% experienced adequate relief of global IBS symptoms in weeks 3–6, compared with 31.7% on placebo (P<.001; the NNT with rifaximin to achieve adequate symptom relief was 11). More patients taking rifaximin experienced improvement in IBS-related abdominal pain and discomfort and had adequate relief of IBS-related bloating in weeks 3–6. Significantly more patients in the rifaximin group reported adequate relief of global symptoms at 3 months (P<.001).

Bottom line: A course of rifaximin improved symptoms over 3 months, but it is unclear how effective this treatment would be over the long term, or how the medication would be used in this chronic, relapsing disease. Nonetheless, rifaximin appears to be a useful short-term option.

How do we pick PURLS?

We scour sources that cover 500 journals daily for useful research evidence, and meet weekly to critically appraise and discuss studies that meet our criteria.

Here are our criteria:

- Relevant: Is the topic relevant to family medicine?
- Valid: Are the findings scientifically valid?
- Change in practice: Would this change practice?
- Medical care setting: Is this implementable in clinic, etc?
- Implementable: Can we implement this immediately?
- Clinically meaningful: Are results clinically meaningful?

<table>
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<tr>
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Bottom line: LNG-IUS is already being used in practice to decrease heavy menstrual bleeding, so even if the study had shown clinically meaningful outcomes (which it did not), these findings would not lead us to a change in practice.

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Use of PPIs before conception increases risk of birth defects


This cohort study of 840,968 live births in Denmark assessed the correlation between exposure to proton-pump inhibitors (PPIs) and birth defects using a National Health Service database. Women who filled a prescription for a PPI from 4 weeks prior to conception through the first trimester were matched with a birth defect registry.

A significant increase in the incidence of defects occurred—from 2.6% to 3.4%—when a PPI was filled at any point during this interval (adjusted OR, 1.23, 95% CI, 1.05–1.44; NNH, 125). When PPI exposure occurred after conception, the incidence of birth defects was similar to those never exposed to a PPI (3.2% vs 2.6%, OR, 1.10; 95% CI, 0.91–1.34). However, when PPI exposure occurred 1–4 weeks prior to conception, major birth defects were significantly increased (3.9%) compared with the group not receiving a PPI (2.6%, adjusted OR, 1.39; 95% CI, 1.10–1.75; NNH, 77).

Bottom line: This study reinforces current recommendations to reserve PPIs only for gastroesophageal reflux disease (GERD) refractory to other treatments in pregnancy. PPIs may be safe after conception from the standpoint of birth defects, but they are still a less preferred option than H2 blockers or lifestyle changes, because of concerns of increased infection and fracture risk, particularly with long-term use. It would also be prudent to reserve PPIs for recalcitrant GERD in patients who are planning to become pregnant.

Another potential use for aspirin


This meta-analysis included 8 RCTs (~25,000 patients) in which long-term aspirin was given to patients for primary or secondary vascular prevention. Investigators reanalyzed the data to assess cancer-related mortality, using individual patient data when possible. Minimum duration of aspirin use was a mean of 4 years in each trial.

Risk of in-trial cancer-related death was decreased in patients receiving aspirin (327/14,035, or 2.3%) compared with patients not taking aspirin (347/11,535, or 3.0%, P=.003). Pooled OR of cancer death was 0.79 (95% CI, 0.68–0.92) and an NNT with aspirin to prevent 1 cancer death within the time frame of the study was 141. In the 3 trials in which outcomes were obtained at 20 years, relative risk of death over the extended time frame from solid cancers was 0.8 (95% CI, 0.72–0.88). No cancer-related mortality benefit was seen in hematologic cancers. This study did not assess overall mortality, morbidity, or adverse effects of aspirin.

Bottom line: The patients in this study were taking aspirin to study its use for cardiovascular prevention. Even though cancer prevention is a different indication, it would not be a change in practice to recommend aspirin for these patients, and its benefit in patients without cardiovascular disease or risk factors is unknown. Only cancer-related mortality was studied by the investigators, which is insufficient to give a true sense of the risk-to-benefit tradeoff for this use of aspirin.
Evidence-Based Answer

H2-receptor antagonists (H2RAs) and proton-pump inhibitors (PPIs) are both effective in the treatment of reflux symptoms when compared with placebo. PPIs are at least twice as effective as H2RAs in achieving remission in the empirical treatment of heartburn and in the treatment of endoscopic-negative reflux disease (ENRD). Treatment with twice-daily PPIs is slightly more effective than once-daily PPIs in the treatment of reflux symptoms among patients with esophagitis (all statements SOR: A, based on meta-analyses).

A 2010 Cochrane systematic review compared the efficacy of short-term (≤12 weeks) use of PPIs and H2RAs in adults with gastroesophageal reflux disease (GERD) symptoms treated empirically. The primary outcome was heartburn remission, defined as patients having heartburn symptoms no more than 1 day per week. In 2 RCTs (with 760 patients) the efficacy for inducing remission in absolute terms with empiric treatment with PPIs versus placebo was 45.2% (95% CI, 0.38–0.52; NNT=2). In contrast, the efficacy of heartburn remission with empiric treatment with H2RAs was 14.0% (2 trials, 1,013 patients; 95% CI, 0.079–0.20; NNT=7).

The same 2010 meta-analysis reviewed the efficacy of PPIs and H2RAs in achieving heartburn remission in those with known ENRD. With both medication classes, the risk reduction of heartburn was greater than placebo but lower than with empiric treatment of GERD symptoms. For treatment of ENRD, the efficacy of heartburn remission with PPIs was 24.6% (8 trials, 2,626 patients; 95% CI, 0.22–0.28, NNT=4) and with H2RAs was 13% (2 trials, 511 patients; 95% CI, 0.050–0.22, NNT=7.5).

A 2009 Cochrane review showed that PPIs improve heartburn remission rates in patients with endoscopic-proven esophagitis. After 4 weeks of therapy, PPIs had an efficacy of 32.8% compared with placebo (1 trial, 320 patients; 95% CI, 0.28–0.42; NNT=3). The review found no studies comparing H2RAs with placebo for reflux treatment in this population.

The same 2009 Cochrane review evaluated the heartburn remission efficacy of standard-dose, once-daily PPIs versus high-dose, twice-daily PPIs among patients with endoscopic-proven esophagitis. In direct comparison trials, high-dose PPI was 6.9% more effective than standard-dose PPI for heartburn remission at week 4 in patients with esophagitis (6 trials, 9,877 patients; 95% CI, 0.050–0.088; NNT=14.5).

What is the work-up of an asymptomatic murmur in adults?

Evidence-Based Answer

Echocardiography is recommended in asymptomatic adult patients with murmurs that are diastolic, continuous, early-systolic, late-systolic, or holosystolic; associated with an ejection click; or midsystolic and grade 3 or louder. Cardiology referral or echocardiogram is also recommended if the examiner cannot characterize the murmur. (SOR: C, based on expert opinion.)

The characteristics of a murmur on auscultation along with the presence or absence of symptoms determines the need for further diagnostic testing. The diagnostic accuracy of cardiac auscultation was assessed in a prospective study of 100 consecutive patients referred for systolic murmur of unknown origin. Two cardiologists blinded to the patient’s history performed a cardiac examination, which was then compared with the results of the echocardiogram.

The diagnostic accuracy of skilled examiners varied from 70% to 97%, depending on the underlying pathology (TABLE). The clinical examination was best for detecting ventricular septal defects (4 of 4 patients), mitral valve prolapse (10 of 11 patients), and isolated aortic stenosis (13 of 15 patients), but limited in other conditions and when more than 1 type of lesion was present. The authors recommended performing an echocardiogram for all patients when clinical uncertainty was present.
A retrospective cohort study focused on referrals for echocardiogram for systolic murmurs. Consecutive echocardiograms were performed on 529 patients (mean age 26.5 years; 54% female) and found normal echocardiograms in 96%, 93%, and 54% of patients with suspected clinically benign murmur, murmur in pregnancy, and other nonspecific murmurs, respectively. The highest prevalence for normal echocardiograms was in the 20-to-29 age group (80%) and lowest in patients older than 60 (11%).

The American College of Cardiology/American Heart Association guidelines recommend echocardiography in adults with murmurs that are diastolic, continuous, early-systolic, late-systolic, or holosystolic; associated with an ejection click; or mid-systolic and grade 3 or louder. Young asymptomatic patients with mid-systolic murmurs of intensity grade 2 or less observed by an experienced clinician do not require further evaluation with electrocardiogram, chest radiography, or echocardiogram. A clinician unsure or inexperienced with cardiac murmurs should consider cardiac consultation to determine the need for an echocardiogram.

**After incision & drainage, are antibiotics indicated for the treatment of uncomplicated abscesses?**

**Evidence-Based Answer**

The use of antibiotics after incision and drainage (I&D) does not improve cure rates compared with I&D alone. This is true even in settings with high rates of methicillin-resistant *Staphylococcus aureus* (MRSA) infection. (SOR: A, based on multiple consistent RCTs.)

Skin and soft tissue infections (SSTIs) are commonly treated with antibiotics after incision and drainage. However, increasing antimicrobial use raises concerns about resistance, adverse effects, and cost. MRSA is a common cause of SSTIs and was cultured from 53% to 80% of abscesses in the 3 RCTs discussed here. In these studies, treatment failure was defined as a lack of clinical improvement or the requirement of additional interventions due to worsening clinical status.
The first RCT was a noninferiority study comparing antimicrobial treatment with placebo in 161 afebrile, otherwise healthy pediatric patients with abscesses, 80% of which were attributed to MRSA. After I&D, patients received either trimethoprim-sulfamethoxazole (TMP-SMX; 10–12 mg/kg per day TMP) or placebo for 10 days. Compliance rates were low in both arms (46% TMP-SMX and 55% placebo). Failure rates were 5.3% (4/76) in the placebo group and 4.1% (3/73) in the antibiotic group (difference not significant).³

Another RCT assigned 212 afebrile, healthy adults with abscesses to either 7 days of TMP-SMX 160 mg/800 mg twice a day or placebo after I&D. There was no significant difference between the groups in failure rates after 7 days (26% in placebo group vs 17% in the antibiotic group (absolute risk reduction [ARR] 9%; 95% CI, –2 to 21; P= .12). MRSA was identified in 53% of these abscesses.³

A third RCT studied 166 outpatient adults with abscesses, including those with comorbidities such as HIV infection, diabetes mellitus, and drug use.⁴ Patients were treated with I&D and cephalexin 500 mg 4 times a day or placebo for 7 days. Clinical cure rate was 90.5% (76/84) in the placebo group and 84.1% (69/82) in the cephalexin group (ARR 6.4%; 95% CI, –4.2 to 17).³ This study was limited by ineffective antibiotic selection for the treatment group, because about 60% of the abscesses were caused by MRSA, which is not susceptible to cephalexin. However, clinical cure rates were high in both groups.

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What is the best way to manage postmenopausal patients with osteopenia?

Evidence-Based Answer  
A retrospective analysis of the subset of osteopenic women (n=3,737; mean age, 68 years) in the Fracture Intervention Trial I and II showed that alendronate 5 mg/d for 2 years then 10 mg/d thereafter (n=1,858) compared with placebo (n=1,859) significantly reduced clinical vertebral fracture rate (risk ratio [RR]=0.40; 95% CI, 0.19–0.76; P= .005) and radiographic fracture (RR=0.57; 95% CI, 0.41–0.81; P= .002) after 4.5 years of follow-up.¹

A retrospective analysis of 620 postmenopausal women with osteopenia (mean age, 64 years) receiving risedronate 5 mg/d (n=311) or placebo (n=309) showed that after 3 years risedronate reduced risk of combined vertebral and nonvertebral fracture by 73% (HR 0.27; 95% CI, 0.09–0.83; P= .023). The cumulative nonvertebral fracture incidence was 5.4% and 0.4%, respectively, for placebo and risedronate (HR 0.09; 95% CI, 0.01–0.71; P= .022) and the cumulative vertebral fracture incidence was 4.2% and 1.8% (HR 0.44; 95% CI, 0.11–1.78; P= .25).⁴

Subgroup analysis of postmenopausal women with osteopenia (n=2,557, mean age, 65 years) in an RCT showed raloxifene 60 mg/d (n=1,287) compared with placebo (n=1,270) significantly reduced risk for new vertebral fracture (RR=0.53; 95% CI, 0.32–0.88) and for new clinical vertebral fracture (RR=0.25; 95% CI, 0.11–0.63). For raloxifene, the NNT to prevent 1 new vertebral fracture was 59 and to prevent 1 new clinical vertebral fracture was 100.³

A prospective cohort study compared the effect of a group exercise regimen of 1-hour duration 3 times weekly for 21 weeks that comprised warm-up, stretching, strengthening, balance, stabilization, and cool-down exercises in 17 postmenopausal women.
with osteopenia (mean age, 55 years) and 16 women with osteoporosis (mean age, 55 years). In women with osteopenia, the mean T-scores increased from −2.7 to −2.4 (P=.006) and the mean BMD increased from 0.67 to 0.72 g/cm² (P=.004). A similar effect was seen in women with osteoporosis.4

The National Osteoporosis Foundation (NOF) guidelines recommend initiating therapy in postmenopausal women and men ≥50 years age with osteopenia and a 10-year hip fracture probability ≥3% or a 10-year major osteoporosis-related fracture probability ≥20% based on the US-adapted World Health Organization absolute fracture risk model (FRAX™; available at www.NOF.org). The NOF recommends weight-bearing exercises, diet and lifestyle modification, and calcium supplementation as first-line interventions for patients with osteopenia.5

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What is the most effective treatment for restless legs syndrome (RLS)?

Evidence-Based Answer

Head-to-head RCTs for the 2 therapeutic agents approved by the US Food and Drug Administration (FDA) for RLS—ropinirole and pramipexole—are lacking. However, pramipexole appears to be more efficacious and may be better tolerated. (SOR: B, based on an “indirect” meta-analysis of placebo comparison trials.)

Dopamine agonists are recommended as first-line treatment. Ergot-derived dopaminergic agents have well-documented cardiac adverse effects and lead to an augmentation phenomenon (worsening of symptoms) in nearly three-quarters of RLS patients with prolonged use. Two nonergot-derived dopamine agonists (NEDAs), ropinirole and pramipexole, have a more favorable adverse-effect profile, and are FDA approved for this indication.1

Treatment studies for RLS often use 1 or more of the following outcome measures. The Clinical Global Impression-Improvement scale (CGI-I) requires the clinician to assess how much the patient’s illness has improved or worsened relative to a baseline state (1=much improved; 7=much worsened). The International RLS Study Group Rating Scale (IRLS) is based on a 10-question self-administered patient survey with total scores ranging from 0 to 40; higher scores represent more severe and frequent symptomatology. The 100-point Medical Outcomes Study (MOS) sleep scale reflects both the quantity and quality of sleep from the patient’s perspective.2

A meta-analysis of 14 placebo-controlled RCTs (n=3,197) of NEDAs was performed. NEDA use resulted in greater likelihood of symptomatic improvement (RR 1.4; 95% CI, 1.2–1.5; P<.001) and greater reductions in IRLS scores (weighted mean difference [WMD] −4.9 points; 95% CI, −6.4 to −3.4; P<.001) from baseline versus placebo. Meta-regression analysis showed a significant inverse relationship between study duration and reduction in IRLS score from baseline.2

A 2009 meta-analysis pooled data from 6 RCTs to evaluate the efficacy of ropinirole. In these similarly designed studies, 1,679 patients were randomized for at least 12 weeks of treatment. At the end of 12 weeks, ropinirole-treated patients slept a average of 2.5 h/wk more, or roughly a 2-fold greater improvement in the nightly quantity of sleep, compared with patients receiving placebo (P<.001).3

A 2008 meta-analysis evaluated the efficacy and tolerability of pramipexole versus ropinirole. The direct meta-analysis confirmed superior efficacy for both treatments versus placebo based on change in IRLS score (pramipexole: −5.5 points; 95% CI, −7.7 to −3.2; ropinirole: −3.2 points; 95% CI, −4.3 to −2.1) and CGI-I scores from baseline (pramipexole: OR 3.0; 95% CI, 2.1–4.3; ropinirole: OR 2.0; 95% CI, 1.5–2.6). An indirect medication comparison (using a probability of ≥95%) found a superior reduction in the mean IRLS score (−2.3 points; 95% credibility interval, −4.2 to −0.41) with pramipexole and significantly lower incidence of nausea, vomiting, and dizziness compared with ropinirole.4

Continued
A more recent RCT evaluated 357 patients (pramipexole 178, placebo 179) for 12 weeks of treatment. \(^5\) At 12 weeks, the adjusted mean change from baseline was significantly greater for pramipexole vs placebo for IRLS score (–13 vs –9.6; \(P<.01\)) and MOS sleep disturbance score (–25 vs –17; \(P=.0008\)).

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

Evidence-Based Answer
Metformin use in patients with diabetes who have a creatinine concentration between 1.5 and 2.5 mg/dL has not clearly been shown to worsen renal function or increase the risk of lactic acidosis. (SOR: \(B\), based on a small RCT and cohort studies.) Still, clinical caution is advised, as rare serious adverse outcomes are hard to study.

Metformin is a first-line treatment for patients with type 2 diabetes mellitus and has been shown to reduce total mortality in this population. However, metformin is thought to increase the risk of lactic acidosis and is considered contraindicated in patients with renal insufficiency.

A 2010 Cochrane review studied prospective and retrospective cohort trials assessing the risk of lactic acidosis with metformin use in patients with type 2 diabetes. In this review, a total 96,295 participants were followed for 125,941 patient-years. The incidence of metformin-associated lactic acidosis was 4.3 per 100,000 patient-years, compared with 5.4 per 100,000 patient-years in the non-metformin group. \(^1\)

However, only 53% of the studies reviewed allowed the inclusion of patients with renal insufficiency (defined as having a serum creatinine concentration >1.5 mg/dL), which involved 37,360 patient-years of metformin use. Therefore, most patients in the review did not have an elevated creatinine level and an assessment for the worsening of renal function or association of renal failure and lactic acidosis could not be made. \(^1\)

A 2002 randomized trial followed patients with elevated serum creatinine and continued metformin use. This study randomly assigned 393 metformin-treated patients with diabetes who developed the contraindication of an elevated creatinine concentration (1.49–2.49 mg/dL) to either continue metformin (198 patients) or discontinue metformin (195 patients). The average creatinine at baseline was 2.14 mg/dL in the metformin group and 2.11 mg/dL in the discontinuation group. The serum creatinine increased to 2.44 mg/dL (16%) in the discontinuation group and to 2.35 mg/dL (10%) in the metformin group (difference not significant). The plasma lactate concentration level increased from 1.5 mmol/L in both groups to 1.61 mmol/L in the metformin group and 1.63 mmol/L in the discontinuation group (difference not significant) over a 4-year period. In this study, there were no cases of lactic acidosis. \(^2\)

In 2001, a retrospective cohort study of 1,847 adult patients with type 2 diabetes evaluated the use of metformin after the development of contraindications—including renal insufficiency. During the 30-month study, 88 patients developed renal insufficiency and 66 of those patients (75%) were either continued or started on metformin. Out of the total study population, there was only 1 episode of lactic acidosis in 4,600 patient-years, and that 1 episode was attributed to a myocardial infarction. No patients with renal impairment developed lactic acidosis. \(^3\)

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References
Geriatrics diagnostics: Dizziness

Dizziness is a symptom of several underlying conditions. It is the most common complaint of older adults, accounting for more than 8 million outpatient visits per year in the United States.

Differential diagnosis

- Dizziness and syncope
  - Good history will help you distinguish the 2 symptoms, which is of utmost importance
  - Usually underlying cardiovascular disease

- Vertigo
  - Commonly due to vestibular disorders
    - 40%-50% Peripheral disorders: involve inner ear or 8th cranial nerve
    - 10%-20% Central vestibular disorders: result in vertical nystagmus
    - 15% Psychological disorders: including anxiety, somatization, and depression

- Presyncope
  - 25% include a number of etiologies: metabolic and cardiovascular disorders, ischemic heart disease, postural hypotension, seizures

- Disequilibrium disorder
  - Gait and balance difficulties, feeling of unsteadiness with a clear head
  - Presbyastasis: interplay of dizziness with age-related physiologic changes

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Editor: Melissa M. Stiles, MD, University of Wisconsin-Madison, Madison, WI

Medial epicondylar apophysitis

Also known as "little leaguer’s elbow," this continuum of damage to the elbow of immature throwing athletes due to valgus strain and varus compression is an overuse injury.

- Can significantly reduce incidence of this injury by:
  - Pitch counts
  - Not throwing the baseball while hurting
  - Attention to proper mechanics while pitching

Pathophysiology

- Pathology
  - Several ossification centers exist in pediatric elbow
    - Appearance starts at 1–2 years of age with capitellum
    - Remaining 5 structures (below) appear approximately every 2 years
    - Most are fused by mid-teen years
    - Order of appearance:
      - Mnemonic: CRITOE
        - Capitellum
        - Radius
        - "Internal" or medial epicondyle
        - Trochlea
        - Olecranon
      - "External" or lateral epicondyle

- Prevalence
  - Elbow pain occurs in 26% of baseball pitchers over 2 seasons
  - Radiographic evidence of medial apophysitis reported in as high as 100% of little league pitchers
  - Actual incidence of little leaguer’s elbow is unknown
    - Many athletes do not seek medical attention
    - Pitch count education has decreased incidence of the condition

Authors: Brent Messick, MD, and Kevin Burroughs, MD, Cabarrus FMRP, Concord, NC

Editor: Carol Scott, MD, U of Nevada, Reno, NV

Additional information can be found at:
www.fpin.org/page/purlsoverview
Cesarean to reduce mother-to-child transmission of HIV

Bottom line
Mother-to-child transmission (MTCT) is the major cause of HIV infection in children. In addition to antiretroviral therapy, cesarean delivery prior to rupture of membranes can reduce transmission. However, postpartum morbidity after cesarean section is greater for women with HIV than for women without HIV. Thus, cesarean section is recommended to reduce HIV infection of newborns if HIV viral loads are high. Vaginal delivery is recommended when maternal HIV viral loads are <1,000 copies/mL, because vertical HIV transmission is rare in such cases. Women with HIV should be informed and involved in planning their route of delivery.

Evidence summary
More than 2,000 children worldwide are infected with HIV every day, and approximately a half million children die annually from its complications.1 Most children <15 years with HIV were infected through MTCT.2 Antiretroviral therapy has been shown to reduce MTCT.2 The risk of MTCT of HIV without any intervention is approximately 25%.3 The risk of MTCT with maternal antiretroviral therapy in pregnancy and labor and neonatal antiretroviral therapy for 6 weeks is 5% to 8%.3 The risk of MTCT with antiretroviral therapy and cesarean delivery prior to rupture of membranes is approximately 2%.3

A 2000 American College of Obstetricians and Gynecologists (ACOG) Committee Opinion recommends that elective cesarean be offered to women with viral loads of >1,000 copies/mL. The cesarean would generally be scheduled at 38 weeks to decrease the risk of rupture of membranes prior to scheduled delivery. The recommendation for cesarean to reduce MTCT was based on evidence from 2 prospective cohort studies, an international RCT, and a meta-analysis of 15 prospective cohort studies with more than 7,800 women/infants. The recommendation that a cesarean not be done for viral loads of <1,000 copies/mL is based on studies in which 0 of 141 children born to women with a viral load of <1,000 copies/mL were infected with HIV.3

Studies of cesarean for women with and without HIV demonstrate higher infectious, bleeding, and other risks for women with HIV.4,5 A study of 45 women with HIV with 450 matched controls found a statistically significant increased risk of anemia, fever, urinary tract infection, and pneumonia among HIV-positive women.5 Sixty-five percent of HIV-positive women had a post-cesarean complication.5 Women with a CD4 count >500 x 10^6 lymphocytes/liter had higher rates of complications.5

A 2005 Cochrane review looked at benefits versus risks of cesarean for women with HIV and concluded, like ACOG, that cesarean before rupture is indicated to prevent MTCT, unless viral loads are low.1 The Cochrane review included 1 RCT and 5 observational studies and looked at both minor morbidity (eg, fever, urinary tract infection) and major morbidity (eg, endometritis, venous thromboembolism). The Cochrane review found that women with HIV who had an elective cesarean section (ECS) had higher rates of minor and major postpartum morbidity (PPM) than those who had a vaginal delivery.1 Women with HIV who had a nonelective cesarean section had an even higher rate of PPM.1 However, most of the PPM was minor. The Cochrane review concluded that while ECS is recommended for women with higher viral loads, it is unclear whether the increased PPM with ECS outweighs the benefits when viral loads are low.

The RCT cited in the Cochrane review compared 183 women with HIV who delivered by cesarean section with 225 who delivered vaginally. The risk of postpartum fever was 6.7% with cesarean delivery versus 1.1% with vaginal delivery (P<.002). The NNT (cesareans needed to prevent 1 MTCT HIV) is 20. The NNH (cesareans to cause 1 postpartum fever) is 20.6 Most would agree that preventing neonatal HIV infection is worth the price of a postpartum fever.

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REFERENCES
Dosing enoxaparin for DVT prophylaxis in morbidly obese patients

Bottom line
Evidence is currently limited on the optimal dosing and frequency of chemoprophylaxis for deep vein thrombosis (DVT) in the morbidly obese hospitalized patient. Increasingly, low-molecular-weight heparin (LMWH) is dosed BID in these patients. One cohort study, conducted in patients with a body mass index (BMI) above 50 kg/m\(^2\) undergoing bariatric surgery, found that LMWH 40 mg every 12 hours resulted in fewer DVT or PE events than 30 mg every 12 hours, without increasing bleeding events.

Review of the evidence
Many hospitalized patients have at least 1 risk factor for venous thrombus embolism (VTE), with 1 common risk factor being obesity.\(^1\) While chemoprophylaxis is recommended to prevent DVT or pulmonary embolism (PE) in at-risk hospitalized patients, optimal dosing is unknown in patients who are morbidly obese. An antithrombotic and thrombolytic guideline by the American College of Chest Physicians does not make any mention of the treatment for the morbidly obese population.

A 2002 prospective study examined the efficacy of DVT prophylaxis in 481 morbidly obese patients (BMI >50 kg/m\(^2\)) undergoing primary or revisional bariatric surgery. All patients received early ambulation, graduated compression stockings, intermittent pneumatic compression, and enoxaparin (LMWH) in 1 of 2 doses. The first 92 patients received LMWH 30 mg every 12 hours, while the remaining 389 patients received LMWH 40 mg every 12 hours. The LMWH was administered 2 hours prior to surgery and continued every 12 hours until the patient was fully ambulatory or until hospital discharge. In the group receiving 40 mg, 0.6% (2/389) had a postoperative DVT or PE compared with 5.4% in the group receiving 30 mg (5/92; \(P<.01\)). There was 1 bleeding episode in each group.\(^2\)

A 2009 observational study examined the specific complications of DVT and PE in the perioperative course of bariatric surgery, and the frequency of dosing of chemoprophylaxis with LMWH. The review looked at 3,122 bariatric procedures performed at 38 German hospitals from January 2005 through December 2007. Patients had a mean BMI at least 48 kg/m\(^2\). Throughout the study period, 87% of patients received chemoprophylaxis once daily and 11.5% received chemoprophylaxis 2 times daily (no specific dose provided).\(^3\)

During the first year of the study, there was no association between BMI and frequency of LMWH dosing, but during the last 2 years of the study, patients with twice-daily dosing with LMWH showed a significantly higher BMI (once daily, BMI=47.7 kg/m\(^2\); twice daily, BMI=51.9 kg/m\(^2\); \(P<.001\)). The overall incidence of postoperative DVT and postdischarge PE was 0.06%, but this study did not differentiate between the 2 doses.\(^3\)

<table>
<thead>
<tr>
<th>Consider twice-daily dosing for deep vein thrombosis chemoprophylaxis in patients undergoing bariatric surgery who have any of the following characteristics(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index &gt;50 kg/m(^2)</td>
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<tr>
<td>Age above 50</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Venous insufficiency</td>
</tr>
<tr>
<td>Hypoventilation syndrome</td>
</tr>
<tr>
<td>Smoking</td>
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<tr>
<td>Thrombosis in medical history</td>
</tr>
</tbody>
</table>

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Corey Lyon, DO
Research FMR
Kansas City, MO

REFERENCES


We invite your questions and feedback.
Email us at EBP@fpin.org.
Is capsaicin effective for neuropathic pain?

**Bottom line**

With repeated application of a low-dose cream or a single application of a high-dose patch, capsaicin is an effective treatment option for neuropathic pain. (SOR: B, based on a meta-analysis and RCTs.) Estimates of benefit and harm are not robust due to limited amounts of data for different neuropathic conditions and inconsistent outcome definitions.

**Evidence summary**

A 2009 Cochrane review on topical capsaicin for treatment of chronic neuropathic pain in adults included 6 RCTs from 1989 to 2008 with 389 patients. Clinical improvement was defined as at least a 50% reduction in pain or equivalent measure. Treatment with 0.075% topical capsaicin cream applied 2 to 3 times daily for 6 to 8 weeks was more effective at decreasing pain than placebo (41% pain reduction with capsaicin vs 26% with placebo; \(P=.001\)).

In 2 studies (n=709) comparing a single application of a capsaicin 8% patch with placebo with 12 weeks of follow-up, the capsaicin patch led to greater pain reduction (39% vs 30% for placebo; \(P=.003\)).

A 2008 multicenter, double-blinded RCT involving 307 patients compared an 8% capsaicin patch (the active group) with a 0.04% capsaicin patch (the control group) for the treatment of a chronic neuropathic pain. Patients were assigned to apply either 1 active or control patch for 30, 60, or 90 minutes on the day of treatment. This was the only patch applied for the duration of the study. A numeric pain rating scale (NPRS) was used to assess average pain scores over the prior 24-hour period from weeks 2 through 12. Week 1 scores were not used because patients were allowed to use a rescue pain medication during that time.

A single 8% patch resulted in better pain reduction than the low-dose patch (22.8% vs 10.7%, \(P=.0026\)) during weeks 2 through 12. Adverse skin reactions were more common with the high-dose patch (72% vs 55%; \(P\) not reported).

An open-label pilot study assessed an 8% capsaicin patch for HIV-associated distal sensory neuropathy. Patients rated pain using an 11-point NPRS and recorded daily pain scores over the prior 24-hour period from weeks 2 through 12. Week 1 scores were not used because patients were allowed to use a rescue pain medication during that time.

The decrease from baseline for pain over the prior 24 hours was 40% (95% CI, 19–61; \(P=.002\)) or −2.4 points on the NPRS (95% CI, −3.9 to −0.9; \(P=.006\)). Sixty-seven percent (8/12) of patients were considered treatment responders, reporting at least a 30% decrease in pain from baseline. Limitations included small sample size, lack of control group, possible nonuniformity of subject population with regard to disease status and therapy, and a wide range of severity in baseline pain scores.

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**REFERENCES**


**GLOSSARY**

<table>
<thead>
<tr>
<th>ARR</th>
<th>absolute risk reduction</th>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>LOE</td>
<td>level of evidence</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NNH</td>
<td>number needed to harm</td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
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<tr>
<td>SOR</td>
<td>strength of recommendation</td>
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