CME

Evidence-Based Practice

Answering clinical questions with the best sources

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IN DEPTH

How accurate is MRI for detecting breast cancer in high-risk women?

Bottom line

In high-risk women between the ages of 40 and 47, breast magnetic resonance imaging (MRI) detects all forms of breast cancer, with a sensitivity of 51% to 100% and a specificity of 75% to 98%, yielding a wide positive predictive value (PPV) range of 7% to 79%. Compared with mammography, MRI demonstrates an overall higher sensitivity for detection of invasive breast cancers, whereas mammography consistently has a higher sensitivity for ductal carcinoma in situ (DCIS). The American Cancer Society (ACS) recommends annual MRI along with mammography in protocols for screening high-risk women.

Evidence summary

In 2008, a systematic review analyzed 11 prospective studies comparing MRI, mammography, and MRI with mammography.[1] Studies varied in size from single-center, single-encounter screening to large multicenter studies with repeated annual screening. High-risk women varied in definition, but included carriers of known BRCA1, BRCA2, or other gene mutations associated with hereditary breast cancer, untested first-degree relatives of persons with such gene mutations, family history consistent with hereditary breast cancer, atypical or lobular carcinoma on previous biopsy, or radiation therapy to the chest. Median age range was 40 to 47 years.

A total of 218 cancers were diagnosed in 4,983 women screened. Cancer ranged from in situ disease to tumors larger than 2 cm with nodal spread. All studies used biopsy confirmation as the gold standard for sensitivity calculations. A Breast Imaging Reporting and Data System (BI-RADS) score of 4 or higher was considered a positive imaging result. One study was excluded from meta-analysis because of insufficient data.[1]

Sensitivity and specificity of MRI alone compared with mammography alone and combination MRI/mammography is listed in the **TABLE**. The PPV for MRI alone (available from 10 of 11 studies) ranged from 7% to 79%, for mammography alone (available from 9 of 11 studies) ranged from 8% to 100%, and for the combination of MRI and mammography (available from 8 of 11 studies) ranged from 7% to 79%.[1]

CONTINUED

TABLE

Sensitivity and specificity of MRI and mammography for detecting breast cancer in high-risk women[1]

Screening technique with BI-RADS >4	Sensitivity (95% CI)	Specificity (95% CI)
MRI	75% (62%–88%)	96.1% (94.8%–97.4%)
Mammography	32% (15.9%–93.3%)	98.5% (97.8%–99.2%)
MRI & mammography	84% (70%–97%)	95.2% (93.7%–96.6%)

BI-RADS=Breast Imaging Reporting and Data System; CI=confidence interval; MRI=magnetic resonance imaging.

One prospective multicenter study included in the above systematic review evaluated the efficacy of annual MRI and mammography screening for 1,909 women (mean age 40 years) at high risk for breast cancer, with known BRCA1, BRCA2, TP53, or PTEN mutations.[2] Clinical breast exam (CBE) was performed every 6 months, with MRI and mammography performed annually.

MRI detected 32 of 45 breast cancers, and 18 of 45 were detected by mammography. Of the 27 tumors missed by mammography, 22 were visible on MRI. Using a BI-RADS score of 3 or higher, MRI sensitivity was 71.1% for detection of all breast cancers, including invasive and DCIS. For invasive cancers only, MRI sensitivity was 79.5% and specificity 89.8%. Mammography was found to have a higher sensitivity than MRI for detecting DCIS, 83% vs 17% (*P*=.22), respectively.[2]

Another prospective study included in the above review examined the sensitivities of breast MRI compared with mammography with or without ultrasound.[3] The 445 participants (mean age 41 years) were known BRCA1 or BRCA2 carriers.

During the first screening, the prevalence of cancers detected was 2.7% and the subsequent annual incidence rate was found to be 2.3%. Eighteen of 21 cancers were detected by MRI (sensitivity 86%). By tumor staging, MRI had a sensitivity of 33% for DCIS and 94% for all other groups. Mammography had sensitivity of 33% for DCIS and sensitivity ranging from 43% to 100% for larger tumors. Sensitivity of mammography increased with increasing size of tumor detected, whereas MRI had similar sensitivities regardless of tumor size. MRI and mammography had similar sensitivities for DCIS.[3]

Recommendations from Others

In 2007 the ACS guidelines recommended annual MRI as an adjunct to mammography in breast cancer screening for known BRCA carriers and their first-degree relatives, women with at least a 20% to 25% lifetime risk of developing breast cancer based on family history, women who received chest irradiation between the ages of 10 and 30, and those with other high-risk genetic syndromes.[4]

The ACS found insufficient evidence for or against MRI screening for women with a 15% to 20% lifetime risk, prior history of breast cancer, mammographically dense breasts, or personal history of lobular carcinoma in situ, atypical lobular hyperplasia, or atypical ductal hyperplasia.[4]

The ACS recommends against MRI screening for women with a less than 15% lifetime risk of developing breast cancer.[4] EBP

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REFERENCES

1. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. *Ann Intern Med*. 2008; 148(9):671–679. **[LOE 2a]**
2. Kriege M, Brekelmans CT, Boetes C, et al; for the Magnetic Resonance Imaging Screening Study Group. Efficacy of MRI and mammography for breast cancer screening in women with a familial or genetic predisposition. *N Engl J Med*. 2004; 351(5):427–437. **[LOE 2b]**
3. Hagen AI, Kvistad KA, Maehle L, et al. Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series. *Breast*. 2007; 16(4):367–374. **[LOE 2b]**
4. Saslow D, Boetes C, Burke W, et al; American Cancer Society Breast Cancer Advisory Group. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. 2007; 57(2):75–89. **[LOE 5]**

GLOSSARY

ARR= absolute risk reduction	NNT= number needed to treat
CI= confidence interval	OR= odds ratio
CT= computed tomography	RCT= randomized controlled trial
LOE= level of evidence	RR= relative risk
MRI= magnetic resonance imaging	SOR= strength of recommendation
NNH= number needed to harm	

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Each physician should claim only those hours of credit that he/she actually spent in the activity.

The learning objectives of the *Evidence-Based Practice* newsletter are to become knowledgeable about evidence-based solutions to commonly encountered clinical problems, to understand how ground-breaking research is changing the practice of family medicine, and to become conversant with balanced appraisals of drugs that are currently being marketed to physicians and/or consumers. The editors of this educational material may review studies that discuss commercial products or devices as well as the unapproved/investigative use of commercial products/devices. The editors of this educational material report that they do not have significant relationships that create, or may be perceived as creating, a conflict relating to this educational material.

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From the Editor

Always beautiful produce

Dear EBP Readers,

I went to a farmer's market recently (planning to increase my intake of fruits and vegetables) and discovered that all the produce displays were absolutely lovely. Coming across some particularly tempting oranges, I just had to pick some up. I quickly noticed that the prettiest side of each orange was facing outward. When I turned the oranges over, I found blemishes, scales, soft spots, and a whitish haze that suggested rot was only a day away. Obviously, some unseen hand had been at work here—probably the farmer's.

In the marketplace, it's natural to want to display the best part of your produce. But something similar happens when researchers display their materials in public, too. Let me explain how I know.

In order to reduce the risk of selective reporting of outcomes, the International Committee of Medical Journal Editors (ICMJE) in 2005 began to ask researchers to register trials before starting data collection. Registrants provide information about a study's design, the primary outcome measures, and the power analysis for the primary outcome. In return, the ICMJE member journals will consider the authors' work for publication when it is done.

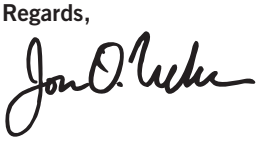
A group of researchers then decided to see how the registration program was going.[1] They discovered that only about half of the studies were adequately registered. But even among those that had been registered correctly, the found the following startling statistics:

- 31% had discrepancies between the primary outcome that was registered and the one that was published
- 10% had the registered primary outcome completely removed from the final manuscript
- 4% had the registered primary outcome demoted to a secondary outcome in the final manuscript

It comes as little surprise that 83% of the time, such irregularities resulted in the final paper highlighting statistically significant results.

So selective outcome reporting remains prevalent, and registries have yet to achieve their full potential. Obviously, this is partly because journal editors have not reviewed the registered information very closely. But maybe they will now, because clearly when the farmers of new knowledge bring their produce to market, they display it with the best bits up.

Regards,



Jon O. Neher, MD

REFERENCE

1. Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. *JAMA*. 2009; 302(9):977–984.

What are the most effective and safest pharmacologic treatments for adults with chronic, primary insomnia?

Evidence-Based Answer

Benzodiazepines (BZDs), nonbenzodiazepine hypnotics (non-BZDs), and antidepressants effectively improve sleep onset latency (SOL), wake time after sleep onset (WASO), and total sleep time (TST). (SOR **A**, based on systematic review/meta-analysis.) Selective melatonin receptor agonists effectively improve SOL, but do not improve WASO or TST. (SOR **A**, based on RCT.) Selective melatonin receptor agonists are the most effective at reducing SOL. (SOR **B**, based on RCT.) BZDs are the most effective at decreasing WASO. (SOR **A**, based on systematic review/meta-analysis.) Antidepressants are the most effective at increasing TST. (SOR **A**, based on systematic review/meta-analysis.)

BZDs, non-BZDs, and antidepressants have an increased incidence of adverse events compared with placebo. (SOR **A**, based on systematic review/meta-analysis.) Non-BZDs are safer (NNH=20) than BZDs (NNH=8). (SOR **A**, based on systematic review/meta-analysis.) Selective melatonin receptor agonists have a safety profile similar to placebo. (SOR **A**, based on RCT.)

No studies directly compare the different classes of medications in terms of efficacy or safety. (SOR **A**, based on systematic review/meta-analysis.)

Evidence summary

Similar efficacy

A 2005 meta-analysis of 67 RCTs (N=7,158) lasting 2 days to 6 months examined the efficacy and safety of BZDs, non-BZDs, and antidepressant medications compared with placebo for the treatment of patients with chronic insomnia.[1] Chronic insomnia was defined by the Agency for Healthcare Research and Quality as insomnia lasting longer than 4 weeks, a long-standing sleep disturbance, or a sleep disturbance requiring participation in a sleep disorder clinic.

BZDs, non-BZDs, and antidepressants effectively improved SOL (amount of time between laying down to sleep and the onset of sleep), WASO (amount of time spent awake in bed after the attainment of sleep), and TST (total time spent asleep while in bed) (**TABLE**).[1]

Non-BZDs had lowest incidence of adverse events

The types of side effects were similar between medication classes and included somnolence, headache, dizziness, nausea, and fatigue. The BZDs, non-BZDs, and antidepressants had significantly greater risk of harm than placebo, with non-BZDs having the lowest incidence of adverse effects (NNH=20) (**TABLE**). No head-to-head comparisons between classes of medications exist.

Non-BZDs better than placebo

Two RCTs of non-BZDs and 2 RCTs of a selective melatonin receptor agonist were published after this 2005 meta-analysis addressing the efficacy and safety of individual medications.

One RCT of eszopiclone (Lunesta) 3 mg versus placebo (N=788) showed efficacy and safety for 6 months of treatment.[2] Eszopiclone effectively decreased patient reported SOL (eszopiclone=–43.6 min, placebo=–33 min, $P<.001$) and WASO (eszopiclone=–39 min, placebo=–22.5 min, $P<.0032$), and increased TST (eszopiclone=+75.9 min, placebo=+35.7 min, $P<.001$).

Over the 6-month period, the all-causality adverse event rates were 81.1% for the eszopiclone group and 70.8% for the placebo group. The most frequent adverse events were unpleasant taste, headache, infection, pain, nausea, and pharyngitis. Adverse event rates were similar after discontinuation of the drug in placebo (10.7%) and eszopiclone (11.2%) groups, none of which represented withdrawal symptoms. Sleep parameters after discontinuation of the medication were not assessed to evaluate recurrence of insomnia.[2]

An open-label extension of the above RCT (N=382) demonstrated sustained improvements in SOL ($P<.05$), WASO ($P<.05$), and TST ($P<.02$) after 12 months of treatment.[3] Among all patients in the open-label phase, the most common treatment-related adverse events were unpleasant taste (6.8%), headache (4.7%), somnolence (3.8%), abnormal dreams (3.0%), and dizziness (2.5%).

TABLE

SOL, WASO, TST, and safety: BZD, non-BZD, and antidepressants compared with placebo[1]

Treatment	SOL decrease, min (95% CI)	WASO decrease, min (95% CI)	TST increase, min (95% CI)	Safety	Cost ($/month)
BZDs (N=2,306, 32 studies)	16.5 (12.5–20.5)	23.1 (10.5–35.7)	39 (27.2–51)	NNH=8	19
Non-BZDs (N=4,527, 29 studies)	18.1 (13.7–22.5)	12.6 (2.3–23)	28 (21.3–34.6)	NNH=20	149
Antidepressants (N=325, 6 studies)	7.4 (4.4–10.5)	11.4 (6.6–16.2)	53.1 (2.8–103.5)	NNH=12	72
Selective melatonin receptor agonists (N=405, 1 study)	32.8	11.8	41.5	N/A	131

BZDs=benzodiazepines; CI=confidence interval; N/A=not available; NNH=number needed to harm; non-BZDs=nonbenzodiazepine hypnotics; SOL=sleep onset latency; TST=total sleep time; WASO=wake time after sleep onset.

Another RCT of eszopiclone 2 and 3 mg versus placebo (N=308) showed efficacy and safety across 6 weeks of treatment.[4] Eszopiclone effectively decreased polysomnographically determined SOL (eszopiclone 3 mg=–24.7 min, 2 mg=–15.5 min, placebo=–8.2 min, *P*<.001 for 2 and 3 mg), WASO (eszopiclone 3 mg=–11.8 min, 2 mg=–10.8 min, placebo=–2 min, *P*<.01 for 3 mg, but not significant for 2 mg), and increased sleep efficiency, defined as the ratio of TST to the total time in bed multiplied by 100 (eszopiclone 3 mg=+7.1%, 2 mg=+5%, placebo=+1.6%, *P*<.001 for 3 mg, *P*<.01 for 2 mg).

The most frequently reported adverse events were unpleasant taste, headache, somnolence, dry mouth, dizziness, back pain, nervousness, and abnormal dreams. The incidence of new adverse events after discontinuation of eszopiclone was less than placebo (eszopiclone 3 mg=15.2%, 2 mg=11.5%, placebo=18.2%, no statistical analysis performed). No difference was noted between groups for central nervous system–related adverse events during the 2-day run-out period.[4]

Single-blind placebo was administered for 2 nights after the treatment period and no rebound was demonstrated with the eszopiclone 3-mg group, whereas the 2-mg group had sleep parameters similar to baseline.[4]

An RCT (N=1,018) evaluating extended-release zolpidem 12.5 mg (Ambien CR) compared with placebo showed patient-reported decrease in SOL (zolpidem=–36 min, placebo=–28 min, *P*<.0014), WASO (zolpidem=–68 min, placebo=–52 min, *P*<.0001), and increased TST (zolpidem=+110 min, placebo=+82 min, *P*<.0001) after 6 months of treatment for 3 to 7 nights per week.[5]

Of the 1,018 patients who received treatment, adverse effects were reported by 63.2% of patients in the treatment group and 51.3% in the placebo group. The most frequent adverse effects were headache, anxiety, somnolence, dizziness, fatigue, disturbance in attention, irritability, nausea, and sinusitis. There was no rebound insomnia after discontinuation of treatment.[5]

During the 3-day washout period, a decreased WASO was sustained in both groups (zolpidem=–35.9 min, placebo=–38.3 min, *P*=.6543). A trend toward improvement in TST was also sustained (zolpidem=+42.9 min, placebo=+49.8 min, *P*=.3969).[5]

Selective melatonin receptor agonist improves SOL, but not WASO or TST

An RCT (n=405) evaluating ramelteon (Rozerem) 8 mg (a selective melatonin receptor agonist) compared with placebo showed a decrease in SOL as measured by polysomnography (ramelteon=–32.8 min, placebo=–22.8 min, *P*=.007) over a 5-week treatment course.[6] WASO and TST in the treatment group were not significantly different from placebo.

Ramelteon had similar incidence of adverse effects compared with placebo, except for somnolence (ramelteon=7.9%, placebo=1.5%), fatigue (ramelteon=9.4%, placebo=2.3%), and nausea (ramelteon=4.3%, placebo=2.3%). Presence of withdrawal symptoms was assessed by the benzodiazepine withdrawal symptom questionnaire (BWSQ) score. The BWSQ scores

between the treatment groups were comparable during the run-out phase. The ramelteon group exhibited a persistent reduction in SOL after treatment discontinuation during the 2-day run-out period.[6]

Another RCT (n=451) evaluating ramelteon 8 mg compared with placebo showed a decrease in SOL as measured by polysomnography (ramelteon=–40.8 min, placebo=–29.5 min, $P<.05$) over a 6-month treatment course.[7] TST in treatment group was not significantly different from placebo.

Ramelteon had a similar incidence of adverse effects compared with placebo (ramelteon=51.8%, placebo=50.7%). No difference was noted between the ramelteon and placebo groups on subjective reports of level of alertness and tests involving immediate and delayed recall. No significant difference was noted in BWSQ scores used to assess the presence of withdrawal symptoms during the 2-week run-out phase. During the 2-week run-out phase, no rebound insomnia was observed.[7] EBP

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REFERENCES

1. Buscemi N, Vandermeer B, Friesen C, et al. Manifestations and management of chronic insomnia in adults. *Evidence Report/Technology Assessment* No. 125. (Prepared by the University of Alberta Evidence-based Practice Center, under Contract No. C400000021.) AHRQ Publication No. 05-E021-2. Rockville, MD: Agency for Healthcare Research and Quality; June 2005. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=hserta&part=A196507. Accessed April 27, 2010. **[LOE 1a]**
2. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep*. 2003; 26(7):793–799. **[LOE 1b]**
3. Roth T, Walsh JK, Krystal A, Wessel T, Roehrs TA. An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia. *Sleep Med*. 2005; 6(6):487–495. **[LOE 2b]**
4. Zammit GK, McNabb LJ, Caron J, Amato DA, Roth T. Efficacy and safety of eszopiclone across 6-weeks of treatment for primary insomnia. *Curr Med Res Opin*. 2004; 20(12):1979–1991. **[LOE 1b]**
5. Krystal AD, Erman M, Zammit GK, Soubrane C, Roth T; ZOLONG Study Group. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. *Sleep*. 2008; 31(1):79–90. **[LOE 1b]**
6. Zammit G, Erman M, Wang-Weigand S, Sainati S, Zhang J, Roth T. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. *J Clin Sleep Med*. 2007; 3(5):495–504. **[LOE 1b]**
7. Mayer G, Wang-Weigand S, Roth-Schechter B, Lehmann R, Staner C, Partinen M. Efficacy and safety of a 6-month nightly ramelteon administration in adults with chronic primary insomnia. *Sleep*. 2009; 32(3):351–360. **[LOE 1b]**

What's in an HDA?

With over 250 manuscripts in process, HelpDesk Answers is the most popular FPIN writing project. HDAs provide high-quality responses to clinical questions, so we've asked Dr. Robert Gauer, author of 10 HDAs, what goes into writing an HDA?

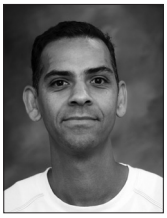
What goes into writing an HDA?

I generally spend about 3 hours performing a literature search. The hardest part is limiting my search. I often find 20 to 30 really good articles that I feel need to be incorporated, but the scope is much more narrow. I get excited about the amount of information that is available.

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 an internal peer review, I am ready to send it off.

My favorite part is the actual writing and seeing how I can take a mountain of information and condense it into a molehill that still has relevance for the reader. Extracting the important stuff and making it truly relevant to our providers who may have a point-of-care question drives me to focus my research and make my answer fit the narrow scope of the question.

I wanted to get our program into research, and writing HDAs is the right fit for our residents. It allows the flexibility and challenge to make it a reachable goal. Also it stimulates residents to ask their own questions, seek out the answers, and get them published. I can't tell you the countless times I have referred to an HDA for a question asked by a student or resident. We found the answer easily, and it took less than 5 minutes to read. A great service to evidence-based medicine!



Robert Gauer, MD has been leading the HDA project with residents at Womack Army Medical Center in Ft. Bragg, NC since 2008. To learn more about what Dr. Gauer is doing with FPIN, please visit http://www.fpin.org/page/Gauer.

DVT prophylaxis in the hospitalized medical patient

Bottom line

Prophylaxis against deep vein thrombosis (DVT) is recommended in acutely ill hospitalized patients, especially those with certain risk factors (**TABLE**). According to the American College of Chest Physicians (ACCP), prophylaxis should be with heparin or heparin-related products, if no contraindications to anticoagulation are present.

Review of the evidence

Venous thromboembolism (VTE)—including DVT and pulmonary embolism (PE)—is an important cause of morbidity and mortality in hospitalized patients, occurring in 10% to 40% of all patients and approximately 10% to 20% of medically ill patients.[1]

A 2007 meta-analysis of RCTs examined the efficacy of VTE prophylaxis in medically ill patients with low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), or placebo.[2] A total of 12,391 patients were examined: 29% had heart failure, 22% had respiratory disease, and 25% had infection/inflammation.

LMWH or fondaparinux significantly reduced DVT events compared with placebo (OR 0.60; 95% CI, 0.47–0.75), with a NNT of 74, and significantly reduced all VTE (OR 0.59; 95% CI, 0.47–0.74), with a NNT of 87. PE events were not significantly reduced (OR 0.54; 95% CI, 0.28–1.05), although the number of events were low. No significant difference was noted between LMWH and UFH in the incidence of DVT (OR 0.92; 95% CI, 0.56–1.52) or VTE (OR 0.89; 95% CI, 0.54–1.46).[2]

Another 2007 meta-analysis of RCTs with 19,958 hospitalized medical patients evaluated DVT prophylaxis versus no prophylaxis.[3]

Anticoagulant prophylaxis was associated with a significant reduction in PE (RR=0.43; 95% CI, 0.26–0.71), with a NNT of 345, and fatal PE (RR=0.38; 95% CI, 0.21–0.69), with a NNT of 400.[3]

A retrospective analysis of a RCT comparing dalteparin 5000 IU with placebo in acutely ill patients for the prevention of VTE examined whether certain groups of medical patients benefit more than others.[4] This study revealed a significant reduction in the primary endpoint of DVT, PE, or sudden death in patients with infectious disease (RR=0.46; 95% CI, 0.25–0.84) and age older than 75 (RR=0.52; 95% CI, 0.31–0.87). The relative risks with prophylaxis were also lower in patients with heart failure and respiratory failure, but these were not significant (RR=0.73; 95% CI, 0.44–1.21 and RR=0.72; 95% CI, 0.38–1.34, respectively). The initial study was not powered to detect significant differences of VTE in individual subgroups.

TABLE

Risk factors for VTE[1]

• Acute infection
• Congestive heart failure
• Acute respiratory disease
• Inflammatory bowel disease
• Previous VTE
• Older age (>75 years)
• Immobility, lower extremity paresis
• Obesity (BMI>30 kg/m^2)
• Central venous catheterization
• Cancer
• Nephrotic syndrome
• Inherited or acquired thrombophilia
• Estrogen therapy (OC, HRT)
• Pregnancy, postpartum period
• Recent surgery or trauma

BMI=body mass index; HRT=hormone replacement therapy; OC=oral contraception; VTE=venous thromboembolism.

Recommendations

A 2008 evidence-based guideline from the ACCP recommends thromboprophylaxis with LMWH, UFH, or fondaparinux for acutely ill medical patients admitted to the hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have 1 or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease (ACCP Grade 1A, strong recommendation with high quality of evidence).[1] EBP

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REFERENCES

1. Geerts WH, et al; for the American College of Chest Physicians. *Chest.* 2008; 133(6 suppl):381S–453S. **[LOE 1a]**
2. Kanaan AO, et al. Meta-analysis of venous thromboembolism prophylaxis in medically ill patients. *Clin Ther.* 2007; 29(11):2395–2405. **[LOE 1a]**
3. Dentali F, et al. *Ann Intern Med.* 2007; 146(4):278–288. **[LOE 1a]**
4. Cohen AT, et al; for the PREVENT Medical Thromboprophylaxis Study Group. *Vasc Med.* 2007; 12(2):123–127. **[LOE 1b]**

The HelpDesk Search Strategy

HelpDesk Answers are intended to provide the same quality response to a clinical question as would be achieved by a search-savvy physician spending an hour or so on the Internet. Authors of HelpDesk Answers are directed to search Healthlinks (http://healthlinks.washington.edu/search_evidence) and the TRIP database (www.tripdatabase.com). These portals provide access to more than a dozen sources of the highest quality evidence-based clinical information, including BMJ Clinical Evidence, the Guide to Clinical Preventive Services, AHRQ Evidence Reports, and others. Searches of the Cochrane Database, Medline, and other databases, are conducted as needed.

What is the minimum number of days of antibiotic treatment for patients hospitalized with acute uncomplicated pyelonephritis?

Evidence-Based Answer

There is no significant difference in clinical cure or tolerability between short-course (7–14 days) and long-course (>14 days) antibiotics for acute uncomplicated pyelonephritis in adults. (SOR **A**, based on a meta-analysis.) A recent guideline from the American College of Obstetricians and Gynecologists (ACOG) recommends 14 days of antibiotic therapy, although there is limited evidence that 7-day therapy may be as effective in premenopausal women. (SOR **B**, based on an RCT.)

In a meta-analysis of acute pyelonephritis studies, 4 RCTs (1 was double-blind, 3 were open-label) were reviewed, involving 199 patients, with most patients being adult women (66%–100%).[1] The age range of subjects was 16 to 94 years (mean age 60 years).

No significant differences in clinical success were found between short (7–14 days) and long (14–42 days) courses of antibiotic treatment for acute pyelonephritis (OR 1.27; 95% CI, 0.59–2.70). This same meta-analysis found no difference in tolerability of short- versus long-course antibiotic treatment (OR 0.64; 95% CI, 0.63–3.06). A variety of different antibiotics were used in the RCTs.[1]

An older RCT from 2000 compared the efficacy and safety of a 7-day ciprofloxacin regimen and a 14-day trimethoprim-sulfamethoxazole regimen for the treatment of acute uncomplicated pyelonephritis in 255 premenopausal women.[2]

Bacteriologic cure rates (defined as pathogen growth <10^4 colony forming units on posttherapy follow-up) were higher for the ciprofloxacin group than the trimethoprim-sulfamethoxazole group (99% vs 89%; *P*=.004). Clinical cure rates (defined as absence of all signs and symptoms of illness through posttherapy follow-up) were also higher for the ciprofloxacin group than the trimethoprim-sulfamethoxazole group (96% vs 83%; *P*=.002).[2]

A meta-analysis of 15 RCTs with 1,743 patients, ages 1 month to 75 years, assessed the mode of administration of antibiotic therapy for severe urinary tract infection (UTI; defined as a syndrome of fever, bacteriuria, pyuria, and clinical symptoms of UTI).[3] This analysis, which contained no double-blind studies, and only 1 single-blind study, reviewed the effect on cure rate, reinfection rate, and kidney scarring.

In this analysis, a small study of 38 patients found a higher bacteriological cure with parental therapy compared with oral therapy (OR 1.37; 95% CI, 1.02–1.84). However, switch therapy (IV initially followed by oral) showed no significant difference in bacterial eradication (RR=0.79; 95% CI, 0.54–1.15) or clinical cure (RR=1.01; 95% CI, 0.94–1.10) when compared with therapy administered entirely by IV. Duration of therapy in the 2 treatment groups was usually equivalent and consistent with short-course therapy, varying between 4 and 14 days.[3]

A recent evidence-based guideline from ACOG on the treatment of urinary tract infections in nonpregnant women recommends 14 days of total antimicrobial therapy regardless of whether therapy is inpatient or outpatient (ACOG Level A, based on good and consistent evidence).[4]

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1. Kyriakidou KG, Rafailidis P, Matthaiou DK, Athanasiou S, Falagas ME. Short-versus long-co urse antibiotic therapy for acute pyelonephritis in adolescents and adults: a meta-analysis of randomized controlled trials. *Clin Ther.* 2008; 30(10):1859–1868. **[LOE 2a]**
2. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial. *JAMA.* 2000; 283(12):1583–1590. **[LOE 1b]**
3. Pohl A. Modes of administration of antibiotics for symptomatic severe urinary tract infections. *Cochrane Database Syst Rev.* 2007; (4):CD003237. **[LOE 1a]**
4. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 91: Treatment of urinary tract infections in nonpregnant women. *Obstet Gynecol.* 2008; 111(3):785–794. **[LOE 2a]**

Should antibiotic prophylaxis be used for cirrhotic patients hospitalized with gastrointestinal bleeding?

Evidence-Based Answer

Yes. Antibiotic prophylaxis in cirrhotic patients with upper gastrointestinal bleeding (UGIB) significantly reduces the incidence of bacterial infections and mortality for up to 30 days of follow-up. (SOR **A**, based on a systematic review.) Norfloxacin for 7 days is recommended (SOR **C**, based on consensus guidelines), although local resistance patterns may make other antibiotics more effective. (SOR **C**, extrapolated from a single comparative RCT.)

The most recent meta-analysis is a 2002 Cochrane review of 11 RCTs involving 1,267 hospitalized patients with cirrhosis who presented with UGIB.[1] The authors performed an extensive search for all published and unpublished RCTs without any restriction to any specific antibiotics or to any specific bacterial infections. Follow-up did not exceed 30 days. The source of UGIB was confirmed by endoscopy. Eight trials (864 patients) compared the effects of an antibiotic group to a placebo group or no intervention.

Antibiotic prophylaxis significantly prevented bacterial infections (RR=0.40; 95% CI, 0.32–0.51, NNT=4), including bacteremia, pneumonia, spontaneous bacterial peritonitis, and urinary tract infections, regardless of the antibiotic used. Three trials (503 patients) compared 1 antibiotic with another. No antibiotic regimen was superior to others for managing bacterial infection or preventing mortality. The most common antibiotic class used was the quinolones. Eight trials that included data on mortality found a significant decrease in death (RR=0.73; 95% CI, 0.55–0.95) by the end of the follow-up period. No significant heterogeneity was found.[1]

Since the Cochrane review, the International Ascites Club published a consensus statement indicating that cirrhotic patients with UGIB should undergo antibiotic prophylaxis with a quinolone antibiotic such as norfloxacin for up to 7 days to decrease the incidence of infection and improve patient survival.[2] Norfloxacin is a poorly absorbable antibiotic active against aerobic gram-negative bacilli common in the intestinal tract, but not against gram-positive cocci or anaerobic bacteria.

Concerns regarding the emergence of quinolone-resistant gram-negative infections prompted a 2006 RCT comparing oral norfloxacin 400 mg every 12 hours for 7 days with intravenous ceftriaxone 1 g daily for 7 days in 111 patients with advanced liver failure and UGIB.[3] By 10 days of follow-up, 33% of the norfloxacin-treated patients developed infections compared to 11% of the ceftriaxone treated patients (*P*=.03; NNT=5). No difference was noted in either hospital mortality or 10-day mortality between the 2 groups.

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1. Soares-Weiser K, Brezis M, Tur-Kaspa R, Leibovici L. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding. *Cochrane Database Syst Rev.* 2002; (2):CD002907. **[LOE 1a]**
2. Wong F, Bernardi M, Balk R, et al; on behalf of the International Ascites Club. Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. *Gut.* 2005; 54(5):718–725. **[LOE 5]**
3. Fernández J, Ruiz del Arbol L, Gómez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology.* 2006; 131(4):1049–1056. **[LOE 1b]**

Is amnioinfusion beneficial when umbilical cord compression is suspected during labor?

Evidence-Based Answer

When umbilical cord compression is suspected due to either variable fetal heart rate decelerations or from confirmed oligohydramnios, amnioinfusion has been shown to reduce fetal heart rate decelerations, operative cesarean deliveries, APGAR scores less than 7 at 5 minutes, incidence of postpartum endometritis, and low cord arterial pH values. (SOR **A**, based on multiple, consistent systematic reviews of RCTs.)

Variable decelerations of the fetal heart rate during labor are usually attributed to umbilical cord compression, which at times may result from intrapartum oligohydramnios.[1] While usually considered benign, when variable decelerations become recurrent or are severe, they can be associated with fetal distress and often prompt operative delivery.[2]

A 2009 Cochrane review evaluated the effect of amnioinfusion on clinically relevant outcomes in laboring women at risk for cord compression or intrauterine infection. Of the 14 studies included in the review, 4 (227 women) demonstrated a reduction of fetal heart rate deceleration (RR=0.54; 95% CI,

0.43–0.68). Nine studies (953 women) demonstrated a reduction in cesarean section rate (RR=0.52; 95% CI, 0.40–0.69). Amnioinfusion was also associated with a reduction of APGAR scores less than 7 at 5 minutes (7 studies, 828 women, RR=0.54; 95% CI, 0.30–0.97), low cord arterial pH (6 studies, 660 women, RR=0.45; 95% CI, 0.31–0.64), and postpartum endometritis (5 studies, 619 women, RR=0.45; 95% CI, 0.25–0.81).[1] The authors noted that a major weakness of the review was that all studies were small and would not have detected any rare complications of amnioinfusion in the mother.

These findings are consistent with a 2000 meta-analysis that found intrapartum amnioinfusion for oligohydramnios was associated with fewer overall cesarean deliveries (13 studies, 1,487 patients; RR=0.40; 95% CI, 0.23–0.56; NNT=11) as well as improvements in other short-term measures of fetal outcome, including acidemia at birth, fetal heart rate abnormalities, and APGAR scores less than 7 at 5 minutes.[3]

A 2009 RCT of 150 women with moderate-to-severe variable decelerations showed amnioinfusion was associated with significant relief of variable decelerations (absolute risk reduction [ARR]=74.6%; 95% CI, 64.4–84.8; NNT=1) as well as a decrease in the number of cesarean sections performed for nonreassuring fetal status (fetal distress) (ARR=12.0%; 95% CI, 0.019–0.259; NNT=9).[2]

In a 2003 study of 160 women with intrapartum oligohydramnios confirmed by ultrasound with an amniotic fluid index less than 5, amnioinfusion was found to be associated with both a significant reduction in nonreassuring fetal heart tracing (ARR=23.8%; 95% CI, 0.094–0.382; NNT=4) and cesarean sections for fetal distress (ARR=15.0%; 95% CI, 0.046–0.254; NNT=7).[4]

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1. Hofmeyr GJ. Amnioinfusion for potential or suspected umbilical cord compression in labour. *Cochrane Database Syst Rev.* 2010; (4):CD000013. **[LOE 1a]**
2. Regi A, Alexander N, Jose R, Lionel J, Varghese L, Peedicayil A. Amnioinfusion for relief of recurrent severe and moderate variable decelerations in labor. *J Reprod Med.* 2009; 54(5):295–302. **[LOE 1b]**
3. Pitt C, Sanchez-Ramos L, Kaunitz AM, Gaudier F. Prophylactic amnioinfusion for intrapartum oligohydramnios: a meta-analysis of randomized controlled trials. *Obstet Gynecol.* 2000; 96(5 pt 2):861–866. **[LOE 1a]**
4. Amin AF, Mohammed MS, Sayed GH, Abdel-Razik S. Prophylactic transcervical amnioinfusion in laboring women with oligohydramnios. *Int J Gynaecol Obstet.* 2003; 81(2):183–189. **[LOE 1b]**

How long should antibiotic therapy be continued for an uncomplicated, symptomatic lower UTI in an elderly woman?

Evidence-Based Answer

Elderly women with symptomatic lower urinary tract infections (UTIs) should be treated for 3 to 6 days with oral antibiotics. This duration provides better short-term outcomes than 1-day therapy and has long-term outcomes equivalent to 7- to 14-day therapy. (SOR **B**, based on a systematic review of heterogeneous RCTs.)

A 2008 Cochrane meta-analysis of 15 RCTs with 1,644 women compared single-dose, short-course (3–6 days) and long-course (7–14 days) antibiotic treatment for uncomplicated symptomatic UTI in elderly women. Participants were >60 years with acute, uncomplicated lower UTI and a positive urine culture with >10^3 colony forming units and >5 leukocytes/mm^3 in the urine. Studies including other patient populations (men, younger persons, individuals with asymptomatic bacteriuria) were included if they comprised <20% of all participants or if separate data were available for the elderly women.

The review cited 7 studies using the same antibiotic with differing duration and 8 studies that compared different antibiotics for different durations. Treatment regimens included sulfamethizole, trimethoprim, fosfomycin trometamol, cephalexin, and various fluoroquinolones. Six studies compared single-dose treatment with short-term (3–6 days) treatment, 3 studies compared single-dose with longer treatment durations (7–14 days) and 5 studies assessed short-term versus long-term treatment. The quality of the studies was highly variable. Nine of the studies were not blinded; the remaining 6 were either double- or single-blinded.

The findings were as follows:

Single-dose vs short-course treatment: The rate of persistent UTI at ≤2 weeks posttreatment was significantly higher for single-dose therapy compared with short-course treatment (RR=2.01; 95% CI, 1.05–3.84). At >2 weeks follow-up, the rate was similar in both groups (RR=1.18; 95% CI, 0.59–2.32). No significant effect was noted for clinical outcomes.

Single-dose vs long-course treatment: Persistent UTI decreased significantly for long-course treatment compared with single-dose therapy at short-term follow-up (≤2 weeks posttreatment) (RR=1.93, 95% CI, 1.01–3.70), but not at long-term follow-up (>2 weeks) (RR=1.28; 95% CI, 0.89–1.84).

Short- vs long-course treatment: No significant difference was noted in the number of persistent UTIs for patients undergoing short-course treatment compared with long-course treatment within the first 2 weeks (RR=0.85; 95% CI, 0.29–2.47). No difference was noted between the 2 groups at long-term follow-up (RR=0.85; 95% CI, 0.54–1.32). In the subset of studies that compared different durations of the same antibiotic, no significant difference was noted at short- (RR=1.00; 95% CI, 0.39–2.19) and long-term (RR=1.18; 95% CI, 0.50–2.81) follow-up.[1]

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1. Lutters M, Vogt-Ferrier NB. Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in elderly women. *Cochrane Database Syst Rev.* 2008; (3):CD001535. **[LOE 2a]**

What is the best way to manage asymptomatic *Chlamydia* infections found on screening nonpregnant women?

Evidence-Based Answer

Nonpregnant women with *Chlamydia* should be treated with azithromycin or doxycycline. (SOR **A**, based on a meta-analysis.) Alternative therapies include erythromycin, levofloxacin, or ofloxacin, with preference for antibiotics being dispensed on site and directly observed. (SOR **C**, based on consensus guideline.) Further management should include patient-delivered partner therapy (SOR **A**, based on a meta-analysis) and abstinence until 7 days posttreatment for both patient and partners, and retesting at 3 to 12 months after therapy (SOR **C**, based on consensus guideline).

A meta-analysis identified 12 randomized English-language trials (N=1,543) comparing single-dose azithromycin with 7 days of doxycycline for the treatment of patients with genital *Chlamydia trachomatis* infection.[1] The microbial cure rates at 2 to 5 weeks of follow-up were statistically equivalent: 96.5% for azithromycin and 97.9% for doxycycline. Subgroup analysis for multiple variables did not affect the results, publication bias was not evident.

The 2006 Centers for Disease Control and Prevention (CDC) guidelines recommend a single 1,000-mg oral dose of azithromycin or doxycycline 100 mg orally BID for 7 days as first-line therapies.[2] Recommended alternatives include erythromycin base 500 mg 4 times a day for 7 days, erythromycin ethylsuccinate 800 mg 4 times a day for 7 days, ofloxacin 300 mg BID for 7 days, or levofloxacin 500 mg once a day for 7 days. This guideline was developed through a consensus conference of experts using a systematic review of the literature, but level of evidence and strength of recommendation indicators were not assigned.

Further CDC guidelines are not as closely linked to supporting evidence and appear to be based on opinion.[2] To increase compliance, the CDC recommended that medications should be dispensed on site and the first dose should be directly observed. Patients should abstain from sexual intercourse until 7 days after a single-dose regimen or until completion of a 7-day regimen and until sexual partners have been treated.

Citing a high risk of recurrent infections during the next several months after resolution of a *Chlamydia* infection, the CDC recommends that women should be tested for recurrence in the next 3 to 12 months. Patients should refer all partners with whom they had sexual contact in the previous 60 days, or their most recent contact if their least sexual contact was more than 60 days ago. Patient-delivered partner antibiotic therapy is recommended as an option.[2]

A subsequent meta-analysis examined methods of partner notification for any sexually transmitted infection and further supports patient-delivered antibiotic therapy.[3] A search of multiple databases without language restriction identified 6 studies (N=6,000) that compared simple patient referral of partners with patient-delivered partner therapy. All studies had weaknesses in randomization, allocation concealment, or number of dropouts. Compared with patients managed by simple patient referral, patients managed with patient-delivered partner therapy had lower rates of persistent or recurrent infection (summary risk ratio 0.73; 95% CI, 0.57–0.93).

Assuming a 10% incidence of persistent or recurrent infection in patients managed with simple patient referral, the number needed to treat with patient-delivered antibiotic therapy would be 27 to prevent 1 persistent or recurrent infection.[3]

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1. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. *Sex Transm Dis.* 2002; 29(9):497–502. **[LOE 1a]**
2. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep.* 2006; 55(RR-11):38–42. **[LOE 5]**
3. Trelle S, Shang S, Nartey L, Cassell JA, Low N. Improved effectiveness of partner notification for patients with sexually transmitted infections: systematic review. *BMJ.* 2007; 334(7589):354–360. **[LOE 1a]**

Is cinnamon effective for reducing blood glucose in patients with type 2 diabetes?

Evidence-Based Answer

Use of *Cinnamon cassia*, in addition to usual care, may modestly lower blood glucose in patients with type 2 (No SOR, due to apparent conflict between RCTs and meta-analysis results.)

Several studies have evaluated the effectiveness of cinnamon in reducing blood glucose in patients with type 2 diabetes mellitus. In a prospective RCT, 60 patients were divided into 6 groups: groups 1–3 received cinnamon at 1, 3, and 6 g/day for 40 days, respectively; groups 4–6 received the corresponding placebo.[1] Baseline fasting blood glucose (FBG) levels ranged from 205 to 300 mg/dL. Patients receiving insulin were excluded from the study.

FBG reductions were noted in all 3 active groups, ranging from 18% to 29% ($P<.05$), compared to no significant differences in the placebo groups.[1]

Another RCT included 79 patients with a mean baseline HbA1c of 6.8% and FBG level of 161 mg/dL.[2] Patients continued 1 or more oral antidiabetic medications or diet and received either 1 g aqueous cinnamon extract or placebo 3 times daily with meals for 4 months. Patients using insulin were excluded.

A significant reduction was noted in FBG (10.35% ± 13.2%) compared with the placebo group (3.37% ± 14.2%; $P<.038$).[2] Two other smaller RCTs[3,4] failed to find any effect (**TABLE**).

In the most recent RCT, 109 patients with an HbA1c >7% were randomized to usual care or usual care plus 1 g cinnamon daily.[5] After 90 days, HbA1c levels decreased in the cinnamon-treated group by an absolute 0.83%, compared with 0.37% in the control group ($P<.04$).[5]

In stark contrast, a meta-analysis published as a brief report in 2008 identified 5 clinical trials (n=282) and reported data on FBG and HbA1c levels.[6] One of the trials included adolescents with type 1 (n=57) diabetes, whereas the rest included patients with type 2 diabetes.

Subgroup analysis for type 2 trials alone (including the 2 later trials above and 2 negative trials not discussed) revealed that cinnamon was associated with a mean FBG reduction of 17.15 mg/dL (95% CI, –47.58 to 13.27) and a HbA1c increase of 0.01% (95% CI, –0.20 to 0.22). The authors concluded that the use of cinnamon did not significantly alter FBG or HbA1c levels.[6] EBP

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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.

1. Khan A, et al. *Diabetes Care.* 2003; 26(12):3215–3218. **[LOE 1c]**
2. Mang B, et al. *Eur J Clin Invest.* 2006; 36(5):340–344. **[LOE 1c]**
3. Blevins SM, et al. *Diabetes Care.* 2007; 30(9):2236–2237. **[LOE 1c]**
4. Vanschoonbeek K, et al. *J Nutr.* 2006; 136(4):977–980. **[LOE 1c]**
5. Crawford P. *J Am Board Fam Med.* 2009; 22(5):507–512. **[LOE 1b]**
6. Baker WL, et al. *Diabetes Care.* 2008; 31(1):41–43. **[LOE 1a]**

TABLE

RCTs evaluating the effectiveness of cinnamon use in patients with type 2 diabetes

Study design, length	Reference	n	Dose (g)	Results	Statistically significant	Comments
RCT, 3 months	Crawford, 2009[a5]	109	1	Lowered HbA1c	Yes	External validity
Meta-anaysis, 3 months	Baker et al, 2008[6]	282	1–6	No change in FBG or HbA1c	No	May be underpowered. No statistical heterogeneity
RCT, 3 months	Blevins et al, 2007[a3]	58	1	No change in FBG or HbA1c	No	Many exclusions. Baseline HbA1c near goal
RCT, 4 months	Mang et al, 2006[2]	79	3	Reduced FBG by 10.4%. No effect on HbA1c	Yes	Strong evidence. Moderate effect on FBG
RCT, 6 weeks	Vanschoonbeek et al, 2006[4]	25	1.5	No change in FBG, insulin, HbA1c, or oral glucose tolerance	No	Good evidence. No men included. Short study duration
RCT, 40 days	Khan et al, 2003[1]	60	1, 3, or 6	Reduced FBG by 18%–29%; did not measure HbA1c	Yes	Strong effect on FBG

[a]RCTs conducted in US patients with type 2 diabetes. FBG=fasting blood glucose; HbA1c=glycosylated hemoglobin; RCT=randomized controlled trial.

Are complementary and alternative medicines effective for insomnia?

Summary

Valerian improves sleep quality and decreases minutes to fall asleep, while appearing relatively safe. Melatonin reduces the time taken to fall asleep in those with delayed sleep phase syndrome. In seniors, melatonin can also increase the percentage of time spent in bed actually sleeping. Kava and skullcap have been linked to hepatotoxicity, and St. John's wort and chamomile may interact with commonly prescribed medications.

The evidence

Insomnia is found in up to 69% of primary care patients, and many patients choose to use alternative medicines.[1,2] The most common supplements used to treat insomnia include valerian, kava kava, St. John's wort, lemon balm, passionflower, hops, skullcap, chamomile, and melatonin.

Of the herbal supplements, valerian is one of the most widely studied. In animal models, valerian (*Valeriana officinalis*) appears to have benzodiazepine-like effects in the CNS.[1] A 2006 meta-analysis examined 16 RCTs with 1,093 patients who met inclusion criteria. No single sleep quality measure was reported by all 16 studies.

Those taking valerian showed a statistically significant doubling of their chances of sleeping better compared with placebo (RR of improved sleep=1.8; 95% CI, 1.2–2.9). However, study methodology was poor. Diarrhea was a statistically significant adverse outcome in 1 study. The remaining studies found no adverse outcomes, no statistically significant adverse outcomes, or didn't provide safety data.[1]

Kava (*Piper methysticum*) has traditionally been used to treat anxiety, and is also used to treat insomnia. In an RCT, 391 participants with anxiety and insomnia received kava, valerian, or placebo. No significant difference was noted for kava or valerian in Insomnia Severity Index scores, frequency of nighttime awakenings, and time to fall asleep compared with placebo.[3] No adverse events were reported in this study; however, kava has been linked to more than 60 cases of hepatotoxicity.[2]

St. John's wort is used to treat depression, and some evidence suggests it improves insomnia in depressed patients, but no studies were found examining St. John's wort as a treatment of primary insomnia. Further, St. John's wort can decrease efficacy of common medications, such as oral contraceptives and statins.[2]

No scientific evidence currently exists for the use of chamomile, lemon balm, passionflower, hops, or skullcap for insomnia. Chamomile may inhibit cytochrome P450 and interact with high-risk medications such as anticoagulants, antiplatelet drugs, and benzodiazepines. Larger doses of skullcap may cause seizure activity or hepatotoxicity.[2]

Melatonin, a natural hormone secreted by the pineal gland, is one of the most popular nonherbal supplements used for insomnia, and is thought to regulate circadian rhythms. A 2005 meta-analysis of 14 RCTs with 279 participants with a primary sleep disorder compared melatonin with placebo.[4]

Participants taking melatonin had a shorter sleep onset latency by 11.7 minutes (95% CI, –18.2 to –5.2). Participants with delayed sleep phase syndrome fell asleep on average 38.8 minutes faster (95% CI, –50.3 to –27.3). Other study outcomes "favored" melatonin, but these trends did not reach statistical significance. Study heterogeneity limited subgroup analysis of melatonin's effect on sleep efficiency (percent of time spent in bed actually sleeping), except for senior participants, who had significantly greater sleep efficiency compared to younger adults. Ten studies provided safety data; the most common adverse events were headaches, dizziness, nausea, and drowsiness, but no significant differences were noted between melatonin and placebo.[4]

Treatment of insomnia is challenging, and interest in complementary and alternative medicine continues to increase. Further research examining the efficacy and safety of herbs and supplements is necessary to expand treatment options. EBP

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REFERENCES

1. Bent S, et al. *Am J Med.* 2006; 119(12):1005–1012. **[LOE 1a]**
2. Meoli AL, et al. *J Clin Sleep Med.* 2005; 1(2):173–187. **[LOE 2a]**
3. Jacobs BP, et al. *Medicine (Baltimore).* 2005; 84(4):197–207. **[LOE 1b]**
4. Buscemi N, et al. *J Gen Intern Med.* 2005; 20(12):1151–1158. **[LOE 1a]**

What is the safest and most effective form of emergency contraception available in the United States?

Bottom line

Oral progestational therapy is more effective and better tolerated than combined hormonal therapy. A single 1.5-mg dose of levonorgestrel within 120 hours of unprotected intercourse is comparable in efficacy to split-dose levonorgestrel for emergency contraception, but is associated with more headaches. (SOR **A**, based on a meta-analysis.) Insertion of a copper-containing intrauterine device (IUD) is also effective and provides long-term contraception, but may need to be avoided in women at risk for certain health conditions (eg, sexually transmitted diseases). (SOR **B**, based on a Cochrane review of a single randomized trial and extrapolation of a randomized trial.)

Evidence summary

A Cochrane review analyzed 2 randomized trials (N=2,878) comparing levonorgestrel 750 mcg every 12 hours for 2 doses with the older Yuzpe regimen (100 mcg ethinyl estradiol plus 0.5 mg levonorgestrel or 1 mg norgestrel).[1] Levonorgestrel was more effective in preventing pregnancy than the Yuzpe regimen (RR=0.51; 95% CI, 0.31–0.83).

Additionally, several adverse effects were significantly lower in the levonorgestrel group: nausea (RR=0.43; 95% CI, 0.39–0.48), vomiting (RR=0.24; 95% CI, 0.18–0.31), dizziness (RR=0.72; 95% CI, 0.61–0.85), and fatigue (RR=0.61; 95% CI, 0.54–0.70). The incidence of other adverse events (eg, breast tenderness, abdominal pain, spotting/bleeding, headache, and early or delayed menses) was not significantly different between the 2 groups.[1]

The same Cochrane review also described 2 other trials (N=3,830) comparing levonorgestrel 1.5 mg as a single dose with 750 mcg every 12 hours for 2 doses in women who had had unprotected intercourse within 72 to 120 hours. Overall, no significant differences were noted in prevention of pregnancy (RR=0.77; 95% CI, 0.45–1.30) or most side effects, with the exception of more headaches reported in the single-dose group (RR=1.23; 95% CI, 1.04–1.47).[1]

A copper IUD is a highly effective form of emergency contraception and offers the additional advantage of providing long-term contraception.[1] One randomized trial compared a copper IUD with no treatment in 300 women who presented within 4 days of unprotected intercourse. Analysis showed a significantly lower risk of pregnancy (4/200) in women receiving the IUD versus those who did not (22/100) (RR=0.09; 95% CI, 0.03–0.26).

Although the authors of the systematic review did not directly compare IUDs with levonorgestrel, they did compare the efficacy of copper IUDs with mifepristone 50 mg (an emergency contraceptive not available in the United States).[1] Results showed 1 pregnancy in 90 women using mifepristone versus no pregnancies in 95 women receiving a copper IUD (RR=1.51; 95% CI, 0.06–36.67). A comparison of split-dose levonorgestrel versus mifepristone 25 to 50 mg (15 trials; N=3,743) demonstrated 56 pregnancies among 1,809 users of levonorgestrel versus 28 pregnancies among 1,934 users of mifepristone (RR=2.01; 95% CI, 1.27–3.1).

An IUD should be inserted within 5 days after unprotected intercourse.[2] The insertion can be extended beyond 5 days if the timing of ovulation can be estimated, as long as insertion does not occur beyond 5 days after ovulation (cycle days 10–17). Patients with current pelvic inflammatory disease or purulent cervicitis (chlamydial or gonorrheal infection) should not have IUD insertion. Likewise, women with distortion of the uterine cavity or cervical or endometrial cancer should not receive IUDs. However, previous ectopic pregnancy, young age, or nulliparity are not contraindications.[3] EBP

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REFERENCES

1. Cheng L, Gulmezoglu AM, Piaggio G, Ezcurra E, Van Look PF. Interventions for emergency contraception. *Cochrane Database Syst Rev.* 2008; (2):CD001324. **[LOE 1a]**
2. *Selected Practice Recommendations for Contraceptive Use.* 2nd ed. Geneva: World Health Organization; 2004. **[LOE 5]**
3. *Medical Eligibility Criteria for Contraceptive Use.* 4th ed. Geneva: World Health Organization; 2009. **[LOE 5]**

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1. Which of the following hospitalized patients should receive DVT prophylaxis?
- ❑ a. An 80-year-old man admitted for an exacerbation of chronic obstructive pulmonary disease
- ❑ b. A 60-year-old woman admitted for acute systolic congestive heart failure
- ❑ c. A 55-year-old man admitted to the intensive care unit for severe sepsis
- ❑ d. All of the above

2. All of the following statements are true regarding the use of amnioinfusion when umbilical cord compression is suspected due to either variable fetal heart rate decelerations or from confirmed oligohydramnios *except*
- ❑ a. Amnioinfusion has been shown to decrease operative cesarean deliveries
- ❑ b. Amnioinfusion has been shown to decrease APGAR scores less than 7 at 5 minutes
- ❑ c. Amnioinfusion has been shown to increase the incidence of postpartum endometritis
- ❑ d. Amnioinfusion has been shown to decrease low cord arterial pH values

3. Which of the following statements is true about complementary and alternative medicines for insomnia?
- ❑ a. Kava has been linked to renal toxicity in patients with hypertension
- ❑ b. Valerian improved sleep parameters in some, but not all, studies
- ❑ c. Melatonin is broken down to L-tryptophan by the body
- ❑ d. St. John's wort increases the effectiveness of statins

4. Which of the following side effects is less likely to occur with levonorgestrel emergency contraception than with the older Yuzpe method?
- ❑ a. Vomiting
- ❑ b. Breast tenderness
- ❑ c. Delayed menses
- ❑ d. Headache

5. Which of the following statements is true regarding women at high risk for breast cancer?
- ❑ a. MRI alone has a lower sensitivity than mammography alone for detection of breast cancer
- ❑ b. Mammography alone has a lower specificity than MRI alone for detection of breast cancer
- ❑ c. Combination MRI and mammography has a higher sensitivity for detection of breast cancer than either MRI or mammography alone
- ❑ d. Combination MRI and mammography has a higher specificity for detection of breast cancer than either MRI or mammography alone

6. In an otherwise healthy adult hospitalized for pyelonephritis, what antibiotic course is most consistent with guidelines from the American College of Obstetricians and Gynecologists (ACOG)?
- ❑ a. Ciprofloxacin 500 mg po BID for 3 days
- ❑ b. Nitrofurantoin 100 mg po BID for 3 days
- ❑ c. Ciprofloxacin 500 mg po BID for 14 days
- ❑ d. Bactrim DS po BID for 7 days

7. Which of the following statements are correct regarding management of cirrhotic patients with gastrointestinal bleeding?
- ❑ a. Antibiotic prophylaxis is not indicated to prevent spontaneous bacterial peritonitis or reduce mortality
- ❑ b. Antibiotic prophylaxis using a quinolone is always most effective
- ❑ c. Antibiotic prophylaxis reduces mortality and several types of infections in the short term
- ❑ d. Antibiotic prophylaxis is recommended to prevent urinary tract infections, but not spontaneous bacterial peritonitis

8. When should nonpregnant women testing positive and being treated for *Chlamydia* infection undergo testing for recurrence?
- ❑ a. 1 to 2 weeks after treatment completion
- ❑ b. 1 to 2 months after treatment completion
- ❑ c. 3 to 12 months after treatment completion
- ❑ d. No retesting is necessary

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Answer key: 1. d; 2. c; 3. b; 4. a; 5. c; 6 c; 7. c; 8. c

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