Peppermint oil as a therapeutic agent for irritable bowel syndrome

Bottom line
Peppermint oil is a safe and effective therapeutic agent for pain and abdominal discomfort in patients with irritable bowel syndrome (IBS). It should be considered as an adjunct in IBS management, however, as pain is only one component of the clinical picture.

Background
IBS is a chronic, relapsing gastrointestinal disorder without a known structural or anatomical explanation. Mechanisms of altered gastrointestinal motility, smooth muscle spasm, visceral hypersensitivity, and abnormalities of central pain processing have all been implicated.

Many modalities have been used to control IBS symptoms, including bulk-forming agents, prokinetics, antispasmodics, antidepressants, exercise, yoga, stress relief, and diet changes, but evidence supporting many of these methods is limited by relatively poor methodology and inconclusive findings. Generally, a holistic approach is required to improve the overall management of this condition, because no individual intervention has a high success rate.

The use of peppermint oil is a nontraditional therapy that has been studied as an inexpensive and easily attainable adjunct for IBS symptoms. Bench research shows its major constituent, menthol, blocks Ca\(^{2+}\) channels in the gut and decreases smooth muscle spasm. Peppermint oil also has a relaxing effect on the gall bladder and slows orocecal transit time.

Summary of Evidence
Meta-analysis
A review of fiber, antispasmodics, and peppermint oil showed that all 3 of these agents are more effective than placebo in the treatment of IBS. Four studies compared peppermint oil with placebo in 392 adults. Only 26% of the patients randomized to peppermint oil had persistent symptoms compared with 65% receiving placebo (relative risk [RR]=0.43; 95% confidence interval [CI], 0.32–0.59; number needed to treat [NNT]=2.5).

When the 3 studies with the highest methodological quality were considered, the relative risk of persistent symptoms was of a similar magnitude (RR=0.40; 95% CI, 0.29–0.55). Adverse events were reported in
3% of the patients receiving peppermint oil and none in those receiving placebo, but the types of adverse events were not discussed. The NNTs to prevent 1 patient from having persistent IBS symptoms were higher for the other agents considered (11 for fiber and 5 for antispasmodics). Only 2 of the 4 studies with peppermint oil used Rome II criteria to define the presence of IBS.  

Other randomized controlled trials (RCTs)  
A subsequent double-blind RCT was conducted on 90 adults with IBS who took 1 enteric-coated capsule containing 187 mg delayed-release peppermint oil (Colpermin®) or placebo 3 times daily for 8 weeks. Their symptoms and quality of life (QOL) were evaluated at 1, 4, and 8 weeks. An IBS symptoms scale was used in which patients rated the intensity of various symptoms from 0 to 3, with 3 being the worst. Additionally, a standardized QOL assessment was completed by the researcher at weeks 1 and 8.  

By week 8, 42.5% of subjects were free from abdominal pain or discomfort in the treatment group, compared with 22.2% in the placebo group (P<.001). Additionally, the mean intensity of abdominal pain was reduced in the Colpermin group from 1.7 to 0.7 (P<.001). The mean QOL score on a visual analog scale from 0 to 10, with 10 being the best, improved from 4.1 to 4.7 by week 8 in the Colpermin group but worsened from 5.8 to 4.0 in the placebo group (P=.02). After 8 weeks, patients taking peppermint oil showed a statistically significant improvement in the QOL domains of bodily pain, general health, social functioning, and role limitations due to emotional problems. The summary QOL scores, however, were not significantly different.  

The frequency of adverse events was not significantly different between the groups (58% in Colpermin vs 52% in placebo, no P-value given). These adverse events were mild, transient, and well tolerated, with the most frequent being heartburn, headache, and dizziness.  

Colpermin did not improve diarrhea, constipation, or bloating. Significant improvement of abdominal pain and discomfort was only noted by week 8. A major limitation was that almost 30% of the subjects were lost to follow-up. Additionally, the initial mean QOL scores were different in the 2 groups, which is concerning for concealed allocation.  

One RCT not included in the meta-analysis of adults above looked at the effect of peppermint oil for treatment of IBS in children. Fifty children were enrolled who met the Rome criteria for IBS and took 1 or 2 Colpermin capsules, 3 times a day for 2 weeks. The age range was from 8 to 17 years (mean age 12). Outcomes were assessed using the Gastrointestinal Symptom Rating Scale (GSRS), a 15-item scale of IBS symptoms tied to duration, frequency, and impact on daily functioning. Additionally, the severity of pain was ranked from 1 to 5, with 5 being the worst.  

After 2 weeks, 76% of patients receiving peppermint oil had reduced severity of pain associated with IBS, compared with 19% receiving placebo (P<.001). Change of symptoms from “much worse” to “much better” were reported in 71% of the patients receiving peppermint oil, compared with 43% receiving placebo (P<.002). However, the GSRS showed no significant difference between the groups, when summed across the 15 items. Pepperment oil did not alter heartburn, gas, urgency of stools, belching, stool pattern, or stool consistency. Eight children withdrew from the study due to use of antibiotics or inability to swallow pills.  

Clinical application  
According to the above studies, peppermint oil has a significant effect on reducing abdominal pain and discomfort caused by IBS in both adults and children.  

The optimal dosing and duration of therapy are unclear, although a dose of 200 to 400 mg of peppermint oil 3 times a day in an adult and 100 to 200 mg 3 times a day in children 8 years and older appears safe. However, clinicians should remember that, as with all herbals, standardization is lacking between different manufacturers. Additionally, it is important to continue recommending behavior and lifestyle modification along with other interventions, as peppermint oil alone may not have a major effect on QOL in adults or overall symptoms scores in children.

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REFERENCES  
Is saw palmetto helpful for benign prostatic hyperplasia?

**Bottom line**

A recent Cochrane review concluded that saw palmetto is not superior to placebo, although the heterogeneity of products and doses studied makes combining results into a meta-analysis problematic. In direct comparisons, saw palmetto demonstrated efficacy equal to finasteride and tamsulosin, with fewer side effects and lower cost.

**Review of the evidence**

Benign prostatic hyperplasia (BPH) is one of the most common diseases among aging men and is generally treated with alpha-adrenergic blocking drugs, 5-alpha reductase inhibitors, or plant-based agents (phytotherapy), including saw palmetto.

The lipid fraction of the ripe saw palmetto fruit contains an ingredient that inhibits 5-alpha-reductase, preventing the conversion of testosterone to dihydrotestosterone. It does not affect overall prostate size, but appears to shrink the inner prostatic epithelium. Saw palmetto and other herbs commonly used for BPH (rye grass pollen, stinging nettle, pumpkin seed) are also rich in plant sterols and stanols. Beta-sitosterol, a plant sterol, is another common supplement used to treat BPH. Beta-sitosterol is found in high concentrations in saw palmetto, vegetables, rice bran, wheat germ, peanuts, and soybeans.

To evaluate the evidence for saw palmetto in the treatment of BPH, a 2009 Cochrane update reviewed 30 randomized trials including 5,222 subjects. Men (97% white) with a mean age of 64.9 years were followed for an average of 19 weeks. Studies looked at a number of different endpoints, including urinary symptom scores, peak urine flow, and prostate size. No significant difference was noted between saw palmetto and placebo for the treatment of urinary symptoms due to BPH. However, the authors commented on the challenges of reviewing research on a product that is not standardized. In the trials reviewed, the dose of saw palmetto ranged from 80 mg twice daily to 160 mg 4 times daily. Challenges in herbal research also include questions regarding what part of the plant to study (root, fruit, flower or stem), how it is grown, how it is harvested, and how the “active” ingredient is extracted from the plant.
The Cochrane review identified 1 RCT of 1,098 patients that directly compared 320 mg saw palmetto with 5 mg finasteride (a 5-alpha reductase inhibitor) for 6 months. Saw palmetto reduced the International Prostate Symptom Score (IPSS) by 37% and finasteride reduced the IPSS by 39% after 6 months (difference not significant). Two randomized prospective trials in the Cochrane review directly compared 320 mg saw palmetto with 0.4 mg of the alpha-blocker tamsulosin (in a total of 582 patients) and found no significant difference between the 2 in resulting IPSS scores.

A large observational study not included in the Cochrane review evaluated the treatment and outcomes of 2,351 patients in 6 European countries with BPH who presented with new BPH symptoms. After 1 year of follow-up, the percentage of men who had a significant improvement in symptoms was greatest for alpha blockers (68%), followed by finasteride (57%), and then saw palmetto (43%). Another common botanical used for BPH, Pygeum africanum, also had a 43% significant improvement in IPSS scores. Compared with watchful waiting, saw palmetto and P africanum reduced IPSS scores an average of 3 points more and resulted in a better quality of life (phytotherapy increased quality-of-life scores by 1.0, alpha blockers by 1.9).

Evidence of benefit is mixed. However, the Cochrane review established the general safety of saw palmetto, with gastrointestinal adverse effects being the most common (in 4% of patients). Side effects of saw palmetto are generally mild and comparable to placebo. In comparison, the side effects of finasteride include erectile dysfunction, gynecomastia, decreased libido, and decreased ejaculate volume.

A commonly used dose of saw palmetto is 320 mg daily (or 160 mg BID) and a 1-month supply costs approximately $10.39. Finasteride costs approximately $70.00 a month and tamsulosin costs about $143.00 a month (www.drugstore.com). A 2003 Cochrane review pooled 34 studies for meta-analysis to investigate the caries-inhibiting effect of fluorinated mouth rinses in 14,600 children over a period of 2 to 3 years. Of the studies selected, 29 were double-blinded, 3 were blinded, and 4 were unclear as to what outcome assessment was used. The mouth rinses were administered under supervision in school programs at a frequency of 3 to 330 times per year. The fluorides used were acidulated phosphate fluoride (APF), sodium fluoride (NaF), amine fluoride (AmF), sodium monofluorophosphate (SMFP), ammonium fluoride (NH4F), and stannous fluoride (SnF2). When rinsing, 16 of the trials used a concentration of 900 ppm fluoride once or twice per week. Across all studies, concentrations of fluoride varied between 100 and 3,000 ppm in volumes of 5 or 10 mL. Rinse times were between 1 and 2 minutes. There was a 26% reduction of caries found on the surfaces of teeth in children who used fluorinated mouth rinse treatments compared with placebo or no treatment (95% confidence interval [CI], 0.23–0.30; P<.0001).
A 2003 meta-analysis, in which 70 double-blinded studies were pooled, examined the effect of fluoride toothpastes on 42,300 children over a period of 1 to 7 years. Children brushed their teeth with fluoride or placebo toothpaste once or twice daily. The fluoride compounds used were APF, NaF, AmF, SMFP, and SnF2. Concentrations of fluoride varied between 250 and 2,500 ppm. There was a 24% reduction of caries in children brushing with fluoride toothpaste compared with placebo (95% CI, 0.21–0.28; P<.0001).

A 2002 Cochrane review, in which 7 studies were pooled for meta-analysis, evaluated the caries-inhibiting effect of fluoride varnish in 2,790 children over a period of 1 to 4.5 years. Of the studies selected, 3 were double-blinded, 5 blinded, and 1 was unclear as to what outcome assessment was used. Dental professionals applied varnish to the teeth with a small brush, probe, or cotton swab 2 to 4 times per year. The fluoride varnishes studied were sodium fluoride–based (Duraphat®, Lawefluor®, and bifluoride 12) or difluorsilane. Concentrations of fluoride varied between 7,000 ppm (difluorsilane) and 56,300 ppm (sodium fluoride–based varnishes) in a volume of 0.5 mL per child for 1 to 4 minutes. The meta-analysis demonstrated a 46% reduction of caries in children who used fluoride varnish treatments compared with placebo or no treatment (95% CI, 0.30–0.63; P<.0001).

A 2002 meta-analysis, including 23 studies, examined the caries-inhibiting effect of topically applied fluoride gels in 7,747 children over a period of 1 to 4 years. Of the studies selected, 14 were double-blinded, 6 were blinded, and 5 were unclear as to what outcome assessment was used. The gel was administered either by tray or brush 1 to 140 times per year. The fluorides used were APF, NaF, AmF, and SnF2. Concentrations of fluoride varied between 2,425 ppm (SnF2) and 12,500 ppm (AmF and NaF) in volumes of 1 to 4 mL. Teeth were exposed to the fluoride gels between 2 and 12 minutes. Fluoride gels demonstrated a 28% reduction of caries compared with placebo or no treatment (95% CI, 0.19–0.37; P<.0001).

A 2006 Cochrane review of 4 studies investigated whether pit and fissure sealants or fluoride varnishes were superior for preventing dental caries in 317 people over a period of 1 to 9 years. Of the 4 studies, 2 utilized allocation concealment along with randomization. The remaining 2 studies used randomization with an unclear concealment approach. Three of the studies compared fluoride varnishes with pit and fissure sealants directly using either parallel study groups or a split-mouth design. One study compared a combination of fluoride varnish and pit and fissure sealant with fluoride varnish treatment alone. Three different types of sealants were used and applied to both sound and repaired surfaces of teeth. All studies used Duraphat as the fluoride varnish, which was applied twice yearly. Patients using pit and fissure sealants developed fewer caries compared with fluoride varnish after 24 months (risk ratio [RR]=0.75; 95% CI, 0.58–0.95) and 9 years (RR=0.48; 95% CI, 0.29–0.79). Patients using pit and fissure sealant in combination with fluoride varnish developed fewer caries compared with fluoride varnish alone after 24 months (RR=0.36; 95% CI, 0.21–0.61).

What common food additives can cause acute, nonallergic symptoms?

Evidence-Based Answer

Aspartame may be associated with headaches in susceptible individuals (SOR B, based on a small crossover study.) Monosodium glutamate (MSG) is associated with a range of constitutional symptoms; however, with blinding, responses to MSG are rarely consistent. (SOR B, based on a randomized controlled trial [RCT].)

A prospective, crossover trial studied 32 patients who reported headaches after ingesting products that contain aspartame. Participants were randomized to...
receive aspartame (approximately 30 mg/kg per day) or placebo for 7 days and then were switched to the other ingredient. Only 18 patients completed the full protocol. Patients reported headaches on 33% of the days during aspartame treatment, compared with 24% on placebo treatment \((P=.04)\). Patients who were “very sure” prior to the study that aspartame triggered headaches had a headache 37% of the aspartame days and 18% of the placebo days \((P<.001)\). This study was limited by poor follow-up and small sample size.\(^1\)

In a multicenter, double-blind, placebo-controlled, multiple-challenge evaluation of reported reactions to MSG, researchers recruited participants reporting adverse reactions to an Asian meal that they thought contained MSG. Participants were included only if they reported 2 or more of the following symptoms: general weakness, muscle tightness, muscle twitching, flushing, sweating, burning sensation, headache-migraine, chest pain, palpitations, or numbness-tingling. The study had 4 sequential protocols designed to test for consistency of reaction and the effect of taking MSG with food. A total of 132 participants were initially enrolled.\(^2\)

In the first protocol, participants received 200 mL of a citrus-flavored beverage containing either 0 or 5 g of MSG on day 1 and the alternate beverage on the second day. Eighty-six participants reported 2 or more symptoms when MSG, placebo, or both were ingested. Only 28% (37/132) reacted to MSG and not placebo.\(^2\)

Of the 86 patients with any sort of reaction in the first protocol, 69 participated in the second protocol. They were administered 200 mL of a citrus-flavored beverage that had 0, 1.25, 2.5, or 5 g MSG in a random order. Only 28% (19/69) reacted to 5 g MSG and not placebo, and 20% (14/69) had the same symptoms on multiple exposures to MSG.\(^2\)

Of these 33, 12 participants were available for the next protocol where, again on alternate days, they received 5-g tablets of MSG or placebo with water. Of these 12 participants, only 2 had symptoms after MSG but not placebo. Neither of these 2 participants had the same symptoms as after MSG ingestion in the first 3 protocols.\(^2\)

In the last protocol, these 2 participants were given a 5-g pill of MSG with food 3 times for breakfast. These 2 participants reported symptoms after only 1 of the 3 MSG challenges administered, and the symptoms were new.\(^2\)

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Are group visits effective for the treatment of obesity?

**Evidence-Based Answer**

Weight loss therapy consisting of 20 to 30 lifestyle-modification group visits is associated with modest (4–8 kg) weight loss. (SOR A, based on homogeneous randomized controlled trials [RCTs].) For patients who participate in group visits, use of sibutramine (15 mg p.o. daily) and compliance with food journaling are both associated with greater weight loss. (SOR B, based on an RCT and an outcomes study.)

A 1-year RCT of 224 obese adults (body mass index [BMI] 30–45 kg/m\(^2\)) compared the effectiveness of group visits for lifestyle modification with pharmacotherapy for obesity treatment.\(^1\) Participants were randomly assigned to receive 1 of 4 treatments: 15 mg sibutramine, sibutramine with brief counseling, lifestyle-modification group visits, or a combination of group visits and sibutramine. The brief counseling consisted of 8 visits of brief lifestyle counseling with prescription renewal. The lifestyle-modification group visits consisted of 30 ninety-minute sessions with 7 to 10 participants led by trained psychologists, using the LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition) program for weight control for the first 20 sessions. The last 10 sessions used the Weight Maintenance Survival Guide. Combination therapy used the same group visit curriculum as well as 15 mg sibutramine. All participants were prescribed the same diet and exercise regimen.
At the end of 1 year, the sibutramine-alone patients lost 5.0±7.4 kg, the group visit patients lost 6.7±7.9 kg, and the sibutramine and brief counseling group visit patients lost 12.1±9.8 kg (P<.001 for all comparisons in the intent-to-treat analysis). Patients in the combination group who recorded their food intake more frequently (highest third of compliance) lost more weight than participants who did so less frequently (lowest third of compliance) (18.1±9.8 kg vs 7.7±7.5 kg, P=.04).

A 6-month, multicenter RCT designed to compare methods of maintenance of weight loss recruited 1,685 (79% BMI>30) overweight and obese participants to participate in weekly group visits for weight loss. The first part of the study (phase 1) was not randomized and involved helping the patients to lose weight. Phase 2 was randomized, but only dealt with weight maintenance. Phase 1 participants participated in 20 group visits led by nutrition and behavioral counselors. The visits lasted 90 to 120 minutes, and included 18 to 25 participants. Participants attended an average of 72% of group visits.

Mean weight change of attendees was 5.8±4.4 kg, with 69% losing more than 4 kg. Participants also reported an average of 117 minutes of moderate-intensity weekly exercise and 3.7 days of food journaling per week.

Weight loss by groups was as follows: African American men (5.4±7.7 kg); African American women (4.1±2.9 kg); non–African American men (8.5±12.9 kg); and non–African American women (5.8±6.1 kg). Participants who lost more weight (non–African Americans) also attended more sessions, reported more physical activity, and kept more food records when compared with African American participants (P>.0001 for each comparison). This study was limited by the lack of a control group.

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What are appropriate treatment goals for hypertension in the very elderly (≥80 years)?

Evidence-Based Answer
Decreasing blood pressure to less than 150/80 mmHg in the very elderly reduces total cardiovascular event morbidity and mortality by 25%, mainly due to a reduction in fatal cerebrovascular events. Treatment of hypertension in this subgroup does not decrease the morbidity or mortality of coronary heart disease or overall mortality. (SOR A, based on systematic reviews).

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were 80 years and older. The study randomly assigned 3,845 patients with sustained systolic blood pressure greater than 160 mmHg to receive a thiazide diuretic and, if needed, an angiotensin-converting enzyme inhibitor, with a treatment goal of 150/80 mmHg. The results demonstrated a 39% reduction in the rate of fatal stroke (95% CI, 1–62; P=.05). Overall mortality was also reduced in the treatment group (RR=0.82; 95% CI, 0.69–0.99; NNT=48). The rates of congestive heart failure (CHF) were reduced by 64% (95% CI, 42–78; P<.001) and cardiovascular events (stroke, myocardial infarction, or CHF) were reduced by 34% (95% CI, 18–47; P<.001). This trial enrolled a relatively healthy patient population, excluding patients with diagnoses of heart failure, renal disease, dementia, secondary hypertension, or the need for nursing care.

Rates of serious adverse events were lower in the treatment group compared with the control group (358 vs 448 events, P=.001). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) recommends a goal of 140/90 mmHg, regardless of patient age. For patients with additional comorbid diseases, including diabetes mellitus, chronic renal disease, and CHF, the goal of 130/80 mmHg is recommended, regardless of patient age. JNC-7 does not contain an evidence-based recommendation for treatment goals for hypertension in the very elderly. The goal of 140/90 mmHg originated from results of the Hypertension Optimal Treatment randomized trial, which did not enroll patients older than 80 years.

**Evidence-Based Answer**

What are the risks of overtreating hyperlipidemia with statins?

In a double-blind RCT with 10,001 patients with low-density lipoprotein (LDL) concentrations <130 mg/dL and coronary artery disease (CAD), patients were randomly assigned to receive either 10 or 80 mg atorvastatin daily and were followed for a median of 4.9 years. The mean LDL levels during treatment were 77 mg/dL with 80 mg atorvastatin and 101 mg/dL with 10 mg atorvastatin. Treatment-related myalgia was reported by 4.7% of the patients in the 10-mg group and 4.8% of the patient in the 80-mg group (P=.72). The 10-mg group had persistent aminotransferase elevation incidence of 0.2%, whereas the 80-mg group had an incidence of 1.2% (P<.001, number needed to harm [NNH]=100). There were no persistent elevations in creatine kinase in either treatment group. There was no significant increase in adverse events of any type among patients who had LDL levels less than 70 mg/dL.

A secondary analysis of the above study investigated the safety of attaining extremely low LDL levels. Among the 98 patients who achieved LDL levels less than 40 mg/dL (mean 34 mg/dL), no significant increase in rate of withdrawal was noted for adverse events, treatment-related myalgia, or persistent liver enzyme elevation.

A randomized, prospective trial of 8,888 patients compared outcomes in patients with CAD using 80 mg atorvastatin and 20 mg simvastatin. Elevation of liver enzyme levels occurred more frequently in the high-dose atorvastatin group (1.38% vs 0.15% in the simvastatin group, P<.001; NNH=91), but this finding was not related to any increase in clinical liver disease. Myalgias also occurred more frequently in the atorvastatin group (2.2% vs 1.1% in the simvastatin group, P<.001, NNH=81), however, no cases of myopathy occurred in either group. An observational study completed in 2007 investigated the safety of statin use in 6,107 patients identified as having and LDL levels less than 60 mg/dL. Statins were...
prescribed for 60% of patients after the low LDL level was identified. Statin therapy was associated with increased survival and was not associated with increased risk of malignancy, transaminase elevation, or rhabdomyolysis.

A review of pricing information reveals the possible financial implications of “overtreating” hyperlipidemia. Drugstore.com (accessed October 5, 2009) lists prices for a 1-month supply as follows: simvastatin 20 mg $28, atorvastatin 10 mg $90, and atorvastatin 80 mg $130.

Evidence-Based Answer

Do you need to use heparin when initiating warfarin therapy in a patient with atrial fibrillation?

Not all patients being initiated on anticoagulation therapy require a heparin bridge. Patients with known hypercoagulable state should receive heparin during anticoagulation initiation. (SOR B, based on guidelines that incorporate medium-quality evidence.)

During initiation of oral anticoagulation therapy there is a theoretical transient hypercoagulable state created when the vitamin K-dependent anticoagulant proteins C and S are depleted (due to their short half-lives), while the vitamin K-dependent procoagulation factors II and X remain (due to their longer half-lives). Heparin is often used as a “bridge” when initiating warfarin therapy in patients with atrial fibrillation to protect patients from this presumed transient hypercoagulable state.

A small, randomized controlled study of 33 patients (mean age 69 years) with symptoms of atrial fibrillation (lasting >48 hours) looked at changes in the biochemical markers of coagulation activity (prothrombin fragment 1 + 2, D-dimer, and soluble fibrin) during the first 60 hours of anticoagulation therapy with either oral anticoagulation therapy or low-molecular-weight heparin (LMWH). Nineteen patients were randomly assigned to the LMWH group and 14 patients to the oral anticoagulation therapy group. No significant difference was found between the effects of oral anticoagulation therapy and LMWH on the relative changes in the biochemical markers at 12, 36, and 60 hours (P > .2). This small study looked at only the markers of coagulation activity, and not on any clinical outcomes such as clot formation.

An evidence-based guideline by the American College of Chest Physicians on the pharmacology and management of vitamin K antagonists was released in 2004. This guideline’s grading system classifies recommendations as strong (grade 1), when the benefits do/do not outweigh the risks, burdens, or costs; or weak (grade 2), when the individual patient’s values may lead to different choices. Furthermore, the quality of evidence is classified as high (grade A), moderate (grade B), and low (grade C) based on factors such as the study design, consistency of the results, and the directness of the evidence.

This guideline stated that for nonurgent treatment (eg, chronic stable atrial fibrillation), oral anticoagulation therapy can be started safely out-of-hospital without concomitant heparin administration (grade 2B). Of note, the study recommends that patients with known protein C deficiency or another thrombophilic state should have a heparin administered before or at the same time as warfarin (grade 2B).

References:


Should you treat an upper extremity deep venous thrombosis with anticoagulation?

**Evidence-Based Answer**

An upper extremity deep venous thrombosis (DVT) should be treated with low-molecular-weight heparin or unfractionated heparin acutely, and then with oral anticoagulation for at least 3 months. (SOR B, based on an evidence-based guideline with low-quality evidence.) Outcomes in patients managed in this way are similar to outcomes of patients with lower extremity DVTs managed with anticoagulation. (SOR B, based on a comparative cohort study.)

Upper extremity DVT is a relatively rare form of venous occlusive disease, accounting for approximately 4% of all DVTs. Currently, no randomized studies have been published on the need, duration, or intensity of long-term anticoagulation. Recent reviews have shown that approximately 56% of patients with upper extremity DVT were discharged from the hospital with antivitamin K therapy.1

An evidence-based guideline by the American College of Chest Physicians on antithrombotic therapy for venous thromboembolism disease was recently released.2 This guideline’s grading system classifies recommendations as strong (grade 1) or weak (grade 2) based on the benefits, risks, burdens, and the confidence in the estimates of those risks and burdens. In addition, these guidelines classify the quality of evidence as high (grade A), moderate (grade B), and low (grade C) based on factors that include the study design, consistency of the results, and the directness of the evidence.3

The guideline states that the treatment of upper extremity DVT should be similar to that of the treatment of lower extremity DVT. Treatment should be initiated with therapeutic doses of low-molecular-weight heparin or unfractionated heparin and then treatment with anti-vitamin K therapy for at least 3 months (grade 1C). This guideline notes that there is little evidence to support long-term anticoagulation for a first, unprovoked upper extremity DVT.2

A recent prospective study followed 11,564 patients with acute DVT, of which 512 patients (4.4%) had an upper extremity DVT, for 3 months after anticoagulation therapy. Etiologically, 38% of patients (196/512) with upper extremity DVT had cancer and 45% (228/512) had catheter-related DVT.4

No significant differences were noted in major outcomes between patients with upper and lower extremity DVTs receiving the same management (major bleeding: odds ratio [OR] 0.99; 95% confidence interval [CI], 0.54–1.82; recurrent DVT: OR 1.43; 95% CI, 0.79–2.57; pulmonary embolism: OR 1.53; 95% CI, 0.77–3.02). This study suggests that the intensity and duration of therapy does not need to differ for lower and upper extremity DVT.1

A recent small retrospective study of 31 patients with upper extremity DVT was conducted to evaluate postthrombotic syndrome after treatment with anticoagulation for 3 to 6 months. This study followed acute DVT not associated with either malignancy or central venous catheters. At 5-year follow-up, 71% of patients did not have postthrombotic syndrome. Key weaknesses included the small sample size and the lack of a control group.4

**Should you use anticoagulation in an elderly patient with atrial fibrillation?**

**Evidence-Based Answer**

The use of anticoagulation in patients older than 75 years with atrial fibrillation reduces the incidence of stroke and death. (SOR B, based on a randomized controlled trial [RCT] and a cohort study.) Evidence is conflicting concerning whether the risk of severe hemorrhage is increased.

Atrial fibrillation is associated with a 5-fold increase in the risk of stroke, and this risk increases with age.1 Some uncertainty remains, however, about the optimum treatment of elderly patients with atrial fibrillation.
A 2007 RCT involving 973 patients with atrial fibrillation older than 75 years (mean age 81.5) compared warfarin (with a goal international normalized ratio [INR] of 2–3) to aspirin 75 mg and followed for an average of 2.7 years. The warfarin group had fewer primary events (major stroke, arterial embolization, and intracranial hemorrhage) compared with the aspirin group (1.8% vs 3.8%, respectively; relative risk [RR]=0.48; 95% confidence interval [CI], 0.28–0.80). The number needed to treat (NNT) for 1 year to prevent 1 primary event was 50. This study also showed no evidence of increased risk of an intracranial hemorrhage, fatal hemorrhage, or the need for transfusion or surgery when comparing warfarin with aspirin (RR=0.88; 95% CI, 0.46–1.63).¹

In a recent prospective, observational cohort study, 270 patients (mean age 77 years) with chronic nonvalvular atrial fibrillation who received anticoagulation or no anticoagulation were followed for an average of 20 months. Patients with contraindications to oral anticoagulation received aspirin or antiplatelet therapy; patients with at least 1 additional cardioembolic risk factor (apart from age) were offered oral anticoagulation. A total of 160 patients received anticoagulation with warfarin (goal INR of 2–3), 103 received aspirin, and 7 received other antiplatelet therapy.²

Compared with patients not receiving anticoagulation, the anticoagulated patients had a lower rate of annual embolic events (0.75% vs 8.79%, P<.001) and total mortality (3.36% vs 8.24%, P=.023), without significant differences in severe bleeding rate (2.61% vs 1.10%, P=.25). In this study, 70% of patients (189/270) had 1 or 2 additional cardioembolic risk factors in addition to age (mostly hypertension and diabetes).²

A recent observational study involving 472 patients older than 65 years (54% were >75) were followed for 1 year after initiating warfarin for atrial fibrillation. This study assessed the rate of “major” hemorrhage, defined as hemorrhages that were fatal, required hospitalization with transfusion, or involved an intracranial, retroperitoneal, or pericardial site.³

Twenty-six patients sustained a major hemorrhage. The rate of major hemorrhage was 7.2 per 100 person-years (95% CI, 4.9–10.6), and the rate of intracranial hemorrhage was 2.5% (95% CI, 1.1–4.7). Patients older than 80 years had higher rates of bleeding compared with younger patients (13.1 vs 4.8 per 100 person-years, P=.01).³

A 2006 guideline produced jointly by the American College of Cardiology, the American Heart Association, and the European Society of Cardiology recommended the use of anticoagulants for patients who have 2 or more risk factors for stroke (age >75, congestive heart failure, hypertension, diabetes, and previous stroke or transient ischemic attack). The guidelines also stated that patients older than 75 years are at a higher risk of bleeding and can be treated with a lower INR. However, no evidence was presented to support a lower goal.⁴

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Are inhaled corticosteroids effective for patients with chronic obstructive pulmonary disease?

Evidence-Based Answer

In patients with stable chronic obstructive pulmonary disease (COPD), inhaled corticosteroids (ICS) do not decrease the risk of all-cause mortality when compared with or added to nonsteroid inhaled therapy, although they increase the risk of pneumonia. (SOR A, based on 2 meta-analyses.) Combination therapy with ICS and long-acting β₂-agonists (LABA) is associated with a lower incidence of moderate (but not severe) COPD exacerbations and improved health-related quality-of-life total scores. However, the size of these benefits does not reach suggested clinically important minimal differences. (SOR A, based on 2 meta-analyses.)

A 2009 systematic review evaluated the safety and efficacy of combined LABA/ICS vs LABA monotherapy in stable patients (mean age 64 years) with moderate to very severe COPD. The review included 18 randomized control trials (RCTs) with a total of 12,446 patients. LABA/ICS did not decrease the num-
number of severe exacerbations (relative risk [RR]=0.91; 95% confidence interval [CI], 0.82–1.01), all-cause mortality (RR=0.90; 95% CI, 0.76–1.06), respiratory mortality (RR=0.80; 95% CI, 0.61–1.05), or cardiovascular mortality (RR=1.22; 95% CI, 0.88–1.71).\(^1\)

The frequency of moderate exacerbations was significantly reduced with LABA/ICS therapy (RR=0.84; 95% CI, 0.74–0.96; number needed to treat=31). Therapy with LABA/ICS also improved scores on the St. George Respiratory Questionnaire, a quality-of-life instrument validated for COPD (weighted mean difference, –1.9; 95% CI, –2.4 to –1.3; score range 0 to 100), in comparison with LABA alone. However, the size of these benefits did not reach suggested clinically important minimal differences.\(^1\)

The use of LABA/ICS was associated with significantly increased rates of pneumonia (RR=1.63; 95% CI, 1.35–1.98), viral respiratory infections (RR=1.22; 95% CI, 1.07–1.39), and oropharyngeal candidiasis (RR=1.59; 95% CI, 1.07–2.37).\(^1\)

Another large meta-analysis evaluated trials comparing ICS use with control therapy (placebo or non-ICS inhaled medication).\(^2\) The review included 14,426 patients enrolled in 11 RCTs. This review found no difference in 1-year all-cause mortality between patients treated with ICS and patients treated with nonsteroid inhaled therapy (RR=0.86; 95% CI, 0.68–1.09). It also confirmed the association of ICS with increased risk of pneumonia (RR=1.34; 95% CI, 1.03–1.75). Subgroup analysis suggested an increased risk of pneumonia in the following subgroups: highest ICS dose (RR=1.46; 95% CI, 1.10–1.92), shorter duration of ICS use (RR=2.12; 95% CI, 1.47–3.05), patient with FEV1 <40% predicted (RR=1.90; 95% CI, 1.26–2.85), and combined ICS and bronchodilator therapy (RR=1.57; 95% CI, 1.35–1.82).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) evidence-based guidelines for COPD diagnosis, management, and prevention recommends the addition of an ICS to bronchodilator therapy only in patients with severe or very severe disease (stage III or IV) who are having repeated exacerbations (3 in the last 3 years).\(^3\)

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Which symptoms best distinguish unipolar and bipolar depression?

Summary

Individually, irritability and psychomotor agitation are not more strongly associated with bipolar disorder than major depression. However, the longitudinal presence of agitation and retardation (termed “psychomotor disturbance”) is associated with bipolar disorder. Still, the association is modest and experts recommend a probabilistic approach to diagnosing bipolar depression, as well as conducting ongoing assessments for manic or hypomanic episodes.

The evidence

Diagnosing patients presenting in a depressed state as having bipolar disorder or major depression is particularly challenging, as most patients with bipolar disorder present to clinics in a depressed mood, not during a manic episode. Estimates are that 50% of patients presenting with symptomatic bipolar disorder are misdiagnosed in the primary care setting. The current Diagnostic and Statistical Manual of Mental Disorders IV-TR does not provide clinical distinctions between bipolar and unipolar depression.

Researchers studied 2,307 patients with major depression using data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study to determine if self-reported irritability in major depression was associated with features known to be associated with bipolar disorder, such as family history of bipolarity, early onset of illness (<18 years), greater episode recurrence, atypical depression, and lifetime suicide attempts. Approximately 46% of the sample reported irritability in the week preceding the interview. No significant associations were found between irritability and 6 bipolar features. For example, 53% of persons without irritable depressions had a family history of bipolar disorder, whereas 47% of persons with irritable depressions had a family history of bipolar disorder.

Another group of researchers investigated a community sample of adults with bipolar disorder (n=93) or major depression (n=99) to examine if certain clinical findings were more closely associated with bipolar disorder than major depression. Historical features associated with bipolar disorder were a family history of mania/hypomania/cyclothymia, and hypomanic or cyclothymic temperament (i.e., a pattern of alternating between hypomanic or irritable and depressive moods, cognitions, and behaviors).

Psychomotor agitation was found in 56% of participants with major depression and 62% with bipolar depression. Agitation with no psychomotor retardation was more indicative of unipolar depression, while persons with psychomotor disturbance (psychomotor agitation and retardation during depressive episodes), were more likely to have bipolar spectrum features (44% vs 21% for major depression, P<.004).

“Probabilistic” approach to distinguishing between bipolar and unipolar depression

<table>
<thead>
<tr>
<th>Bipolar I depression probable if ≥5 of the following features are present:</th>
<th>Unipolar depression should be considered if ≥4 of the following features are present:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersomnia and/or increased daytime napping</td>
<td>Initial insomnia/reduced sleep</td>
</tr>
<tr>
<td>Hyperphagia and/or increased weight</td>
<td>Appetite and/or weight loss</td>
</tr>
<tr>
<td>Other “atypical” depressive symptoms, such as “leaden paralysis”</td>
<td>Normal or increased activity levels</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>Somatic complaints</td>
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<tr>
<td>Psychotic features and/or pathological guilt</td>
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<tr>
<td>Lability of mood/manic symptoms</td>
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<tr>
<td>Onset of first depression &lt;25 years (early onset also defined as &lt;18 years)</td>
<td>Later onset of first depression (&gt;25 years)</td>
</tr>
<tr>
<td>Multiple prior episodes of depression (≥5 episodes)</td>
<td>Long duration of current episode (&gt;6 months)</td>
</tr>
<tr>
<td>Positive family history of bipolar disorder</td>
<td>Negative family history of bipolar disorder</td>
</tr>
</tbody>
</table>

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Do inhaled beta-agonists control cough in acute bronchitis?

**Bottom line**

The value of inhaled $\beta_2$-agonists in patients with acute bronchitis is unclear and any potential benefit remains unproven. (Two small randomized controlled trials [RCTs] using different agents reached different conclusions.) Beta-agonists may have a role in patients with acute bronchitis who are wheezing. (SOR C, based on expert opinion and subanalysis of an RCT).

**Evidence summary**

**Fenoterol**

A double-blind, randomized, placebo-controlled trial studied the effect of fenoterol aerosol 0.2 mg 4 times daily in adults with acute bronchitis. Patients recorded daily symptoms of day- and nighttime cough, sputum production, dyspnea, chest pain, clamminess, and fatigue and scored each symptom from 0 to 2 in order of severity.

At 7 days, mean decrease in total symptom score from baseline was 67% for fenoterol ($n=37$) and 51% for placebo ($n=36$) ($P=.06$). A significant increase in forced expiratory volume in 1 second was detected with fenoterol versus placebo (5.1% vs 0.5%; 95% confidence interval, 1.4%–7.8%); however, no significant improvement was noted in peak expiratory flow rate (10.7% increase for fenoterol vs 8.1% for placebo, $P$ not given).

At enrollment into the study, 49% of fenoterol users and 47% of placebo users presented with abnormal lung findings suggestive of obstructive lung conditions. Upon stratification, this subset exhibited marked symptom improvement on day 2 (mean decrease in symptom score of 52% for fenoterol vs 10% for placebo; $P$ not given) and day 7 (54% for fenoterol vs 32% for placebo; $P$ not given). Eighteen patients in the fenoterol group reported tremor and 7 reported palpitations. No tremor was reported in the placebo group, and 1 patient reported palpitations.

**Albuterol**

Another RCT evaluated the effectiveness of inhaled albuterol compared with placebo in adults with a productive cough of less than 30 days’ duration and without pneumonia, asthma, chronic obstructive pulmonary disease, or cardiac disease. Patients received either inhaled albuterol ($n=23$) or placebo ($n=23$) plus erythromycin 250 mg or placebo. Primary outcome was resolution of cough after 7 days of treatment; secondary outcomes were percent of patients with productive cough and persistent night cough. Additionally, patients recorded presence of cough, night cough if applicable, ability to perform work, and general well-being.

Significantly more patients in the albuterol group than in the placebo group experienced resolution of cough at 7 days (91% albuterol vs 61% placebo; $P=.02$). After stratification by erythromycin use, the albuterol group continued to demonstrate statistically significant decreases in cough after 7 days compared with placebo (Mantel-Haenszel statistic=4.30, $P=0.04$), independent of the effect of the antibiotics. Due to significant divergence in primary outcomes being achieved after 46 patients, the study was suspended before reaching the intended enrollment of 132 participants. Secondary outcomes such as productive cough present at 7 days (57% albuterol vs 48% placebo) and percentage of patients with persistent nighttime cough (26% albuterol vs 45% placebo) were not significantly different between groups ($P$ not given). Side effects were similar in the groups.

**American College of Chest Physicians recommendations**

The 2006 American College of Chest Physicians guideline on treatment for acute bronchitis recommends against the routine use of $\beta_2$-agonists to alleviate cough (quality of evidence, fair; benefit, none; grade of recommendation, D [negative recommendation]). In patients with wheezing in addition to cough, $\beta_2$-agonists may provide some benefit (quality of evidence, fair; benefit, small/weak; grade of recommendation, C [weak recommendation]).

**REFERENCES**

1. When treatment with combined inhaled corticosteroids and long-acting beta-agonist (ICS/LABA) is compared with LABA monotherapy in patients with severe chronic obstructive pulmonary disease (COPD), which of the following statements is true?
   - a. ICS/LABA therapy decreases the risk of respiratory mortality
   - b. ICS/LABA therapy is associated with a lower incidence of severe COPD exacerbations
   - c. ICS/LABA therapy is associated with a decreased risk of viral respiratory infections
   - d. ICS/LABA therapy is associated with an increased risk of pneumonia

2. Which of the following statements is true regarding the use of peppermint oil for irritable bowel syndrome?
   - a. It reduces the frequency of diarrhea and constipation
   - b. It relieves abdominal pain and discomfort
   - c. It frequently causes acid reflux
   - d. Treatment is given once a day as a liquid

3. Which of the following treatments for prevention of dental caries is associated with the greatest reduction in the incidence of caries?
   - a. Toothpaste
   - b. Mouth rinses
   - c. Varnish
   - d. Pit and fissure sealants

4. Which one of the following statements is most accurate regarding the treatment of benign prostatic hyperplasia (BPH) with saw palmetto?
   - a. Saw palmetto is generally well tolerated
   - b. Saw palmetto is more effective than finasteride
   - c. Saw palmetto is more expensive than tamsulosin
   - d. Saw palmetto is the only herbal product available for BPH

5. Which of the following statements is true regarding diagnosis of bipolar depression?
   - a. Irritability is uniquely associated with bipolar depression
   - b. Patients with bipolar disorder rarely present in clinics in a depressive state
   - c. Psychomotor disturbance is associated with bipolar depression
   - d. Bipolar depression can be reliably diagnosed at presentation using a combination of historical and clinical findings

6. Which of the following adverse events is consistently more common with high-dose statin therapy than low-dose therapy?
   - a. Rhabdomyolysis
   - b. Creatine kinase elevation
   - c. Liver enzyme elevation
   - d. Nausea

7. Which statement is the most accurate regarding benefit provided from treatment of hypertension in the very elderly (≥80 years)?
   - a. According to JNC 7, the treatment goal for the very elderly is <140/90 mmHg
   - b. Pharmacotherapy for hypertension in the very elderly improves coronary heart disease mortality
   - c. Pharmacotherapy for treatment of hypertension in this group decreases the overall stroke risk
   - d. Isolated systolic hypertension in this group should not be treated

8. A relatively healthy 75-year-old woman has just been diagnosed with atrial fibrillation. What is your choice for treatment?
   - a. Do not anticoagulate, the risk for hemorrhage is too great
   - b. Prescribe aspirin 325 mg/d
   - c. Prescribe warfarin with a goal international normalized ratio (INR) of 2–3
   - d. Prescribe warfarin with a goal INR of 1.5–2.0
One group reviewed more than 50 publications, mostly cross-sectional or prospective studies, examining symptom profiles of (a) persons with bipolar disorder compared with major depression, or (b) persons with major depression who later converted to bipolar disorder. They focused exclusively on bipolar I disorder in an attempt to correlate historical and clinical features with the disease. The authors proposed a “probabilistic” approach to the diagnosis of bipolar I depression in a person experiencing a major depressive episode with no clear prior episodes of mania (TABLE). However, the proposed diagnostic algorithm has not been prospectively validated.

Clinical application

Reliable criteria are lacking for distinguishing unipolar (major depression) from bipolar depression, and misdiagnosis remains common. Irritability is not a good discriminator, but psychomotor disturbance should be considered a marker for bipolar features. However, experts continue to recommend using probabilistic criteria and taking a longitudinal approach to unclear diagnoses, particularly in younger age groups, using a provisional diagnosis and monitoring for manic or hypomanic episodes.

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