**What are the best pharmacologic options for prophylaxis of acute mountain sickness (AMS)?**

**Evidence-based answer**

Acetazolamide decreases the incidence of AMS with a number needed to treat of about 6 (SOR: A, meta-analysis of RCTs). Dexamethasone and ibuprofen also decrease the incidence of AMS with NNTs of 3 and 5, respectively (SOR: B, meta-analyses of RCTs with risk of bias).

**Evidence summary**

A 2012 meta-analysis of 24 RCTs (N=1,870) evaluated the prevention of AMS using oral acetazolamide at divided doses of 250, 500, and 750 mg/d (minimum of 125 mg BID). The study did not report demographic information for the included patients. AMS was diagnosed using the Lake Louise Scoring System (LLSS), the Environmental Systems Questionnaire (ESQ), or the General High Altitude Questionnaire (GHAQ). Trials were also grouped by rate of ascent using climbing, transportation to high altitude with and without further climbing, and hypobaric chamber as proxies for ascent rate.

All 3 doses of acetazolamide reduced the incidence of AMS compared with placebo with a consistent relative risk reduction (see TABLE); however, the baseline risk was not consistent among the doses, resulting in NNT differences. As the dose increased, there was a significant increase in some adverse events (polyuria and taste disturbance), but not others (paresthesias). Paresthesias occurred in 68% to 90% of patients treated with acetazolamide versus 9% to 29% with placebo, which could have compromised patient blinding. There was no evidence of heterogeneity or publication bias.

A 2014 meta-analysis of 8 RCTs (N=226) evaluated use of oral dexamethasone versus placebo for the prevention of AMS in adults exposed to altitudes of 2,050 to 4,875 m. The patients had no history of AMS and a permanent residence located below 500 m in 7 trials. One trial included patients with a history of high altitude pulmonary edema. All trials were double-blinded and placebo-controlled, with dexamethasone dosed at 2 to 8 mg orally every 6 to 12 hours. AMS was diagnosed using one of the following standardized scoring systems: LLSS, AMS Sickness Score, AMS Symptom Questionnaire, or an abbreviated ESQ combined with the GHAQ.
In Depth

Prevention of acute mountain sickness with acetazolamide versus placebo by dose and method of ascent

<table>
<thead>
<tr>
<th>Dose</th>
<th>Trials</th>
<th>N</th>
<th>RR</th>
<th>95% CI</th>
<th>AMS in controls</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>125 mg BID</td>
<td>6</td>
<td>603</td>
<td>0.55</td>
<td>0.42–0.74</td>
<td>32%</td>
<td>7</td>
</tr>
<tr>
<td>250 mg BID</td>
<td>12</td>
<td>995</td>
<td>0.50</td>
<td>0.40–0.63</td>
<td>32%</td>
<td>6</td>
</tr>
<tr>
<td>375 mg BID</td>
<td>6</td>
<td>272</td>
<td>0.45</td>
<td>0.34–0.61</td>
<td>61%</td>
<td>3</td>
</tr>
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</table>

Method of ascent (rate of ascent)

<table>
<thead>
<tr>
<th>Method of ascent</th>
<th>N</th>
<th>RR</th>
<th>95% CI</th>
<th>AMS in controls</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Climbing (9–19 m/h)</td>
<td>11</td>
<td>1,475</td>
<td>0.51</td>
<td>0.41–0.62</td>
<td>30%</td>
</tr>
<tr>
<td>Transport ± climbing (28–1,285 m/h)</td>
<td>11</td>
<td>352</td>
<td>0.51</td>
<td>0.40–0.66</td>
<td>59%</td>
</tr>
<tr>
<td>Hypobaric chamber (4,375–4,500 m/h)</td>
<td>2</td>
<td>43</td>
<td>0.45</td>
<td>0.26–0.77</td>
<td>86%</td>
</tr>
<tr>
<td>Overall</td>
<td>24</td>
<td>1,870</td>
<td>0.51</td>
<td>0.43–0.59</td>
<td>37%</td>
</tr>
</tbody>
</table>

AMS=acute mountain sickness; NNT=number needed to treat.

Dexamethasone decreased the incidence of AMS compared with placebo (40% vs 71%; NNT=3; 95% CI, 2–5). Adverse event rates were not reported. Methods of randomization were inadequately described in all trials and an asymmetric funnel plot suggested possible publication bias. There was no evidence of clinically relevant heterogeneity.

A 2014 meta-analysis of 3 RCTs (N=349) evaluated the prevention of AMS using NSAIDs (ibuprofen or calcium carbasalate) versus placebo in adult climbers reaching altitudes of 3,810 to 5,896 m (mean 4,801 m). The patients were 74% male with a mean age of 37 years and a permanent residence below 1,240 m. One trial of ibuprofen (n=232) was at significant risk of selection bias from patient acclimatization prior to enrollment, because patients were recruited after arrival at 2 locations 4,280 m or higher above sea level. AMS was diagnosed using the LLSS. The 1 trial of calcium carbasalate (N=75) was excluded from pooled odds ratio calculation since there were no cases of AMS in either arm of the trial. Ibuprofen (600 mg TID) decreased the frequency of AMS compared with placebo (29% vs 48%; NNT=5; 95% CI, 3–13). There was no evidence of heterogeneity.

REFERENCES


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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the US Air Force at large, or the US Department of Defense.

GLOSSARY

ARR=absolute risk reduction
CDC=Centers for Disease Control and Prevention
CI=confidence interval
CT=computed tomography
FDA=US Food and Drug Administration
HR=hazard ratio
LOE=level of evidence
MRI=magnetic resonance imaging
NNH=number needed to harm
NNT=number needed to treat
NSAID=nonsteroidal anti-inflammatory drug
OR=odds ratio
RCT=randomized controlled trial
RR=relative risk
SOR=strength of recommendation
SSRI=selective serotonin reuptake inhibitor
WHO=World Health Organization

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The obvious conclusion

The pile of unread research journals at home was tall enough to be both a fire hazard and a structural fall risk, so I recently spent part of a rainy Saturday afternoon leafing through them, mainly reading the abstracts. Okay, I was just reading the conclusion sections of the abstracts.

I wasn’t more than 5 minutes into this exercise—still working on the blue journals—when I began to notice a certain phrase repeated over and over in the vast majority of conclusions. Authors were almost uniformly asserting, given the totally amazing outcome just described, that “further research was required.”

I have been reading this phrase ever since I started reading journals, and so (probably) have you. When I was young and naive, I thought it was perhaps expected—maybe you weren’t allowed to publish a research paper without including “further research was required” at the end. It was like Porky Pig stammering, “That’s all folks” at the end of a Looney Tunes cartoon. Later, I began to wonder if this was some sort of secret signal (to the research funders) that the authors would soon be back asking for another grant—job security for scientists.

The truth finally dawned on me (partly because I read it somewhere).¹ Good science always results in more questions than it answers. As the bubble of what is known expands, the area of the unknown just beyond that bubble expands as well.

Suppose I’ve just discovered that penicillin kills Group A Streptococcus. I would then want to know if it could be used clinically for strep throat. Next, I might have questions about the best dose, optimum duration of therapy, best follow-up scheme, and if other antibiotics would work, too. Then I’d want to know how quickly resistance developed and if killing the bacteria improved the rate of rheumatic heart disease. On and on, new questions keep presenting themselves.

So it should be obvious that “further research” is always called for, after every study. In fact, it should be so obvious that “further research was required” at the end. It was like Porky Pig stammering, “That’s all folks” at the end of a Looney Tunes cartoon. Later, I began to wonder if this was some sort of secret signal (to the research funders) that the authors would soon be back asking for another grant—job security for scientists.

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So it should be obvious that “further research” is always called for, after every study. In fact, it should be so obvious that research paper authors can stop saying it. Please!

**Fracture risk increases with subclinical hyperthyroidism**


This meta-analysis of 13 prospective cohort studies (N=70,298) assessed the association between subclinical hyper- and hypothyroid disease and fractures of the hip, spine, and other bones. Fracture incidence in euthyroid patients was compared to that in patients with subclinical hypothyroidism (thyroid-stimulating hormone [TSH] 4.50–19.99 mIU/L) and subclinical hyperthyroidism (TSH <0.45 mIU/L) over a median follow-up of 12 years. The primary outcome was hip fracture, while secondary outcomes included nonspine and spine fractures.

Compared with euthyroid patients, patients with subclinical hyperthyroidism were at higher risk for hip fracture (HR 1.36; 95% CI, 1.13–1.64) and any fracture (HR 1.28; 95% CI, 1.06–1.53). Rates for nonspine fracture (HR 1.16; 95% CI, 0.95–1.41) and spine fracture (HR 1.51, 95% CI, 0.93–2.45) were not significantly different. Results were adjusted for age, sex, body mass index, thyroid medication use, and loss to follow-up.

The risk was not increased in patients with subclinical hypothyroidism for hip fracture (HR 0.96; 95% CI, 0.83–1.10), any fracture (HR 1.02; 95% CI, 0.89–1.18), nonspine fracture (HR 1.06; 95% CI, 0.90–1.24), or spine fracture (HR 0.96; 95% CI, 0.59–1.55). Fracture risk was found to increase with lower TSH levels. For example, hip fracture risk was higher if TSH <0.10 mIU/L (HR 1.61; 95% CI, 1.21–2.15) versus 0.10–0.44 mIU/L (HR 1.34; 95% CI, 1.01–1.77), with \( P=0.001 \) for comparison.

**Bottom line:** Subclinical hyperthyroidism is associated with increased risk of hip fractures; however, further studies are needed to evaluate whether treatment of subclinical hyperthyroidism would lead to decreased fracture rates.

**Review and Summary Author:** Liz Nguyen, MD, The University of Chicago, Chicago, IL

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**Epidural steroid injection or gabapentin for lumbosacral radicular pain**


This RCT compared gabapentin with corticosteroid epidural injection in 145 adults with chronic lumbosacral radiculopathy and leg pain of 6 weeks’ to 4 years’ duration. Patients also had MRI evidence of herniated discs or spinal stenosis. Patients received either 60 mg depomethyprednisolone and bupivacaine by epidural injection with oral placebo gabapentin or sham epidural and oral gabapentin titrated to 1,800–3,600 mg/d.

The primary outcome was average leg pain score (ALPS) measured on a 0-to-10 rating scale (mean score 5.4 at baseline for both groups). Secondary outcomes were average and worst back pain, score on the Oswestry disability index, adverse effects and complications, change in analgesic drug use, and global perceived effect.

At 1 month, leg pain scores had improved for both the epidural injection (ALPS 3.3, mean change from baseline [MCFB] –2.2) and gabapentin (ALPS 3.7, MCFB –1.6) groups, but no significant adjusted difference between groups was noted (mean difference [MD] 0.4; 95% CI, –0.3 to 1.2). At 3 months, the epidural injection (ALPS 3.4, MCFB –2.0) and gabapentin (ALPS 3.7, MCFB –1.6) groups again showed no significant adjusted difference (MD 0.3; 95% CI, –0.5 to 1.2). Secondary outcomes at 1 month showed small differences, which did not persist at 3 months.

Total adverse event rates (excessive pain, fever, infection, falls in the epidural group, and sedation, cognitive dysfunction, and headache in the gabapentin group) were not significantly different.

**Bottom line:** Epidural corticosteroid and oral gabapentin each lead to modest improvement in pain scores in patients with chronic sciatica. Gabapentin 1,800–3,600 mg/d is a reasonable first choice in the primary care setting.

**Review and Summary Author:** Deborah E. Miller, MD, University of Chicago, NorthShore FMR, Chicago, IL

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**Bottom line:** Epidural corticosteroid and oral gabapentin each lead to modest improvement in pain scores in patients with chronic sciatica. Gabapentin 1,800–3,600 mg/d is a reasonable first choice in the primary care setting.
Does exercise reduce falls in older adults living in nursing homes?

Bottom line
The evidence is mixed regarding the efficacy of exercise to prevent falls in older adults living in nursing homes. Combined strength and balance programs lasting 6 months or more, delivered 2 to 3 times a week, may be effective (SOR: C, inconsistent meta-analyses).

Case
During a visit to see a new nursing home patient, the patient’s daughter expresses concern regarding the number of falls her father has had in the past year. She wonders if there is anything he or others can do to prevent further falls.

Evidence summary
Authors of a 2015 meta-analysis of 13 studies, including nearly 23,000 nursing home residents, investigated fall prevention programs in nursing homes. Seven of the 13 studies included physical activity or exercise; most studies used a multidisciplinary approach. Physical activity was defined as strength and resistance, gait, balance and/or functional training.

The meta-analysis failed to show an effect on number of falls per resident year or number of people falling (RR 0.93; 95% CI, 0.76–1.13).1

A 2013 meta-analysis focused on studies specifically designed to assess the effect of exercise on fall prevention in older adults living in nursing homes.2 This analysis of 9 studies, including 1,292 long-term care patients, concluded that exercise was effective to prevent falls if both strength and balance exercises were emphasized (RR 0.71; 95% CI, 0.5–0.90). Additionally, exercise was more effective if implemented for more than 6 months with a frequency of 2 to 3 times per week (RR 0.70; 95% CI, 0.56–0.87).

Authors of a 2012 systematic review of more than 60,000 patients in both hospitals and long-term care facilities found inconsistent results regarding exercise programs to reduce falls.3 Overall, no difference was noted in rates of falls (RR 1.03; 95% CI, 0.81–1.31) or risk of falling (RR 1.07; 95% CI, 0.94–1.23) between exercise and control groups. Similar lack of effect was noted in a subanalysis of patients in long-term care facilities only.

Post hoc analysis by level of care, however, found that exercise might reduce falls in people in intermediate-level facilities. The duration of the 4 intermediate-care studies included in this analysis was 6 to 12 months compared to 4 to 12 months in the high-level nursing care facilities. Post hoc analysis by frailty also found that exercise increased falls in people who were more frail.

A 2011 meta-analysis of 41 RCTs assessed the recruitment, attrition, and adherence of falls prevention programs in institutional settings.4 Of the 41 trials, 15 studies (n=335) were classified as exercise interventions. Of the patients who exercised, there was no significant difference in fall rates between those who adhered to the program and those who did not. This finding was true for all types of exercise, including high intensity, endurance, and tai chi. The authors noted that adherence rates were high for individualized and group-based exercise, although specific rates were not presented.

Case Wrap-Up
The family should be made aware that most studies do not support the use of exercise programs to prevent falls in the long-term care setting. Such programs might actually harm more frail patients. To be effective at all, combined strength and balance training would likely be required several times a week for at least 6 months.

REFERENCES
Is megestrol acetate an effective appetite stimulator in HIV wasting syndrome?

Evidence-Based Answer

Among patients with anorexia-cachexia syndrome, which includes patients with HIV/AIDS, megestrol acetate (Megace®) increases weight gain by 1.9 kg, but does not significantly improve appetite or quality of life (SOR: B, systematic review of RCTs).

Megestrol acetate was approved by the US Food and Drug Administration in 1993 for treatment of anorexia-cachexia syndrome, otherwise known as HIV wasting syndrome, in AIDS patients.1,2

A 2004 systematic review of 26 RCTs examined the effects of megestrol acetate on appetite, weight gain, and quality of life among 3,887 patients with cancer, AIDS, or other pathologies and anorexia-cachexia syndrome.1 Megestrol acetate was compared with placebo, different doses of megestrol acetate, and other medications including prednisolone, dexamethasone, cisapride, dronabinol, and nandrolone decanoate.

For patients with HIV/AIDS, there was an improvement in weight gain (defined as any observed weight gain) compared with placebo (2 trials, n=287; RR 2.2; 95% CI, 1.5–3.2). However, data were insufficient to evaluate appetite and no significant improvements were seen in quality of life (described as improved or not improved) (7 trials, n=1,019; RR 1.6; 95% CI, 0.7–3.9). There were also no significant dose-based improvements in the comparison of ≥800 mg/d to <800 mg/d. Data were insufficient to compare megestrol acetate to other treatments in the subgroup of patients with HIV/AIDS. Edema was the only statistically significant adverse event found with megestrol acetate use among all of the trials (26 trials, n=3,887; RR 1.7; 95% CI, 1.2–2.3).1

Another systematic review, in 2013, examined 35 RCTs for the effect of megestrol acetate on the primary outcomes of weight gain, quality of life, and adverse events.2 Through evaluation of 3,963 patients for efficacy and 3,180 patients for safety with a diagnosis of anorexia-cachexia syndrome in the settings of cancer, AIDS, and other pathologies, megestrol acetate was compared with placebo, different doses, and other medications. A subgroup analysis of the 5 trials that specifically evaluated HIV/AIDS patients did not provide sufficient data for individual results.

Weight gain improved with megestrol acetate in all comparisons among noncancer patients (10 trials, n=1,109; mean difference [MD] 1.9 kg; 95% CI, 0.06–2.9). In patients with HIV/AIDS, megestrol acetate provided no improvement in quality of life compared with placebo (3 trials, n=423; RR 1.5; 95% CI, 0.47–4.7). Both edema (12 trials, n=2,182; RR 1.4; 95% CI, 1.1–1.7) and thromboembolic phenomena (11 trials, n=1,544; RR 1.4; 95% CI, 1.1–3.2) were statistically significant adverse events.2

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Is phenobarbital effective in treating alcohol withdrawal?

Evidence-Based Answer

It may have a role. Adding IV phenobarbital to lorazepam in the emergency department (ED) decreases ICU admissions compared with lorazepam alone, decreases total ED lorazepam dosing, and reduces the need for continuous IV lorazepam. As individual agents, phenobarbital and lorazepam appear to have comparable effectiveness in lowering Clinical Institute Withdrawal Assessment (CIWA) scores in the ED (SOR: B, small RCTs).

One RCT from 2013 evaluated single-dose phenobarbital with benzodiazepines in adults presenting to an ED with alcohol withdrawal severe enough to require admission and treatment with benzodiazepines (N=102).1 Patients were diagnosed with alcohol withdrawal based on physician judgment of the following symptoms: heart rate >100 bpm, tremor, paroxysmal sweats, agitation, anxiety, and hallucinations or clouded sensorium. Investigators excluded patients with severe hepatic impairment, pregnancy, or allergy to study medications.

Patients received 10 mg/kg phenobarbital IV in 100 mL saline or 100 mL IV saline placebo in a double-blind fashion. Both groups subsequently received oral or IV lorazepam for scores of ≥3 on a local modification of CIWA scoring, assessing 6 domains (tremor, sweats, agitation, hallucinations,
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Evidence-Based Answer

Is topical sucralfate an effective therapy for noncandidal diaper rash?

In patients with diaper dermatitis, sucralfate 20% ointment increases the rate of complete healing at 1 week, and decreases mean time to complete healing by 2 days compared with 20% zinc oxide ointment (SOR: C, small RCT). Complete healing with sucralfate 4% cream is equivalent to hydrocortisone cream at 2 and 8 weeks (SOR: C, small RCT).

A 2012, double-blind RCT (N=46) investigated topical treatments for irritant diaper dermatitis in a single hospital in Iran.1 The children had a mean age of 4.4 months, 54% of them were female, and none had been treated with topical therapy in the 2 weeks before enrollment. Children were excluded if secondary infectious dermatitis was present or if they had ever been given an injectable or oral steroid. They also lacked a history of atopic dermatitis, candidiasis, seborrheic dermatitis, or sensitivity to zinc oxide. Enrolled infants were hospitalized to ensure compliance with treatment and assessment protocols. Treatment of patients admitted was not reported.2

CIWA score decreased in both groups from baseline to ED discharge or admission (phenobarbital: from 15.0 to 5.4, P<.001; lorazepam: from 16.8 to 4.2, P<.001). There were no differences between groups in baseline or ED discharge CIWA scores, length of ED stay, or hospital admission rate. One patient in the phenobarbital group returned with a seizure. Follow-up in the ED at 48-hours was low (n=18), but showed no significant differences in CIWA scores, relapse rate, or medication compliance. This study included only patients with mild-moderate alcohol withdrawal in a predominantly Latino population. Enrollment was slightly below goal based on power calculations of 23 patients per group.2

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A 2004, double-blind RCT (N=64) investigated topical treatments for diaper dermatitis in an outpatient dermatology clinic in India. Children had a mean age of 11.3 months, 63% of them were female, and the dermatitis was present for a mean of 1.5 months. Patients with skin fold involvement, satellite lesions, fungus on potassium hydroxide skin scrapings, or a history of treatment with corticosteroids or zinc oxide were excluded. Topical creams of 4% sucralfate or hydrocortisone (unknown potency) were applied 4 times daily for 8 weeks. The area of affected skin was evaluated every 2 weeks, with complete healing defined as more than 50% improvement and partial healing defined as 20% to 50% improvement.

At 2 weeks, sucralfate increased partial healing but the difference was not statistically significant (41% vs 25%; P>.05), and the rate of complete healing was the same in both groups (47%). There were also no differences at 8 weeks, with 91% complete healing and 9% partial healing in both groups. The only reported side effect was mild erythema and dryness in 1 patient treated with sucralfate.

**Evidence-Based Answer**

Overall, psychosocial family interventions for bipolar disorder do not appear to be effective. There is conflicting evidence on symptomatic improvement, medication compliance, and relapses but recovery rates and ratings of family relationships do not appear to improve. Patient-reported anxiety may be increased with psychosocial family interventions (SOR: B, systematic reviews with inconsistent findings).

A 2010 systematic review of studies with “experimental design” looked at the efficacy of various psychosocial interventions as an adjunct to pharmacotherapy for adults with bipolar disorder. Inclusion criteria were psychosocial interventions specific to bipolar disorder, interventions adjunctive to pharmacotherapy, participant age 18 years and older, results focused on patient outcomes, outcome data reported using any measurement instrument, experimental design, and published between 1990 and 2009.

Eight studies, including 611 patients, evaluated family interventions with psychoeducational and family therapy techniques. The results of 4 of the studies were summarized but numerical results for the individual studies were not reported and it was unclear why the 4 other studies were not discussed. One of the 4 highlighted studies involved treatment of 101 patients with bipolar disorder over 9 months at the patients’ or their parents’ home. It involved all available family members with treatment by trained therapists using psychoeducation, communication enhancement, and problem-solving skills.

Compared with crisis management, these family-focused psychointerventions led to fewer relapses, longer delays before relapses, greater improvement in depressive but not manic symptoms, greater reductions in mood disorder symptoms, and better medication adherence. The results from 3 other studies including 274 patients showed no significant improvement with family intervention in regard to disease-free intervals and recurrence of depressive symptoms when compared with pharmacotherapy alone.

A 2007 Cochrane review of 7 RCTs investigated the effectiveness of family psychosocial interventions as an adjunct to pharmacotherapy for the treatment of bipolar disorder. This review had 2 studies in common with the review above but included others for reasons not fully explained by differences in the study inclusion criteria. The trials included 393 patients 18 to 62 years old with a diagnosis of bipolar disorder based on the Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD) criteria, as well as their relatives or caregivers. Five of the studies (n=244) looked at psychosocial family intervention as an adjunct to pharmacotherapy compared with pharmacotherapy alone.

The studies used different family psychosocial interventions and outcome measures, which precluded pooling of results. Interventions focused on psychoeducation about bipolar disorder including acceptance, treatment, coping strategies, and trigger
identification. Primary outcomes included clinical improvement in patients' affective symptoms as measured by standard validated scales and recovery based on symptom rating scales.

Adjunctive psychosocial family interventions did not improve recovery rates (1 study, n=92) or clinical improvement (2 studies, n=65) compared with pharmacotherapy alone. Similarly, no significant differences were noted between groups in the secondary outcomes of medication compliance (1 study, n=39), dropout rates (5 studies, n=244), and ratings of family relationships (1 study, n=45). Patients in the family intervention group had moderately increased levels of anxiety, based on a patient rating scale, when compared with the no-intervention group (1 study, n=39; standardized mean difference 0.69; 95% CI, 0.05–1.3).²

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Does screening smokers for lung cancer using CT improve mortality and morbidity?

**Evidence-Based Answer**

**Probably.** Annual screening with low-dose computed tomography (LDCT) in patients with a 30 pack-year smoking history decreases mortality. False-positive rates are high (SOR: B, based on single RCT).

A 2011 RCT compared LDCT with chest radiograph (CXR) in 53,454 current or former smokers aged 55 to 74 with 30 or more pack-years (median follow-up 6.5 years) to determine if LDCT screening could reduce mortality from lung cancer.¹ Patients were screened annually for 3 years with either LDCT or CXR.

Mortality in the LDCT group was significantly decreased compared with CXR (356 vs 443 deaths, respectively, relative reduction in mortality 20%; 95% CI, 6.8%–26.7%; \( P = .004 \)). The number needed to screen with a 1-time LDCT to prevent 1 death from lung cancer was 320. The LDCT arm had a high rate (96.4%) of false-positive results, which were later shown to be negative with noninvasive follow-up CT scans to check for stability.¹

The other positive RCT (2009) compared usual care with and without annual screening LDCT over 5 years for 2,472 current or former smokers aged 60 to 74 with a smoking history of ≥20 pack-years (median follow-up 33.7 months).² Lung cancer was detected in more patients receiving LDCT than control patients (4.5% vs 2.8%; \( P = .016 \)). This study did not show any significant benefit in mortality (RR 0.82; CI, 0.45–1.54), although this study had fewer patients enrolled, fewer overall lung cancer cases, and a shorter follow-up than the above larger study.

Two other RCTs did not show benefit. One was a 2012 RCT comparing annual LDCT with no lung screening for 5 years in 4,104 subjects 50 to 72 years old with a 20 pack-year history (median follow-up 4.8 person-years).³ This study found no significant mortality benefit (RR 0.85; 95% CI, 0.56–1.27). The other was a 2012 RCT comparing annual and biennial LDCT screening versus usual care in 4,099 current and former smokers ≥49 years old with ≥20 pack-year exposure and who had quit less than 10 years ago.⁴ It found no significant benefit of CT screening between both LDCT groups and the control group in all-cause mortality (RR 1.40; 95% CI, 0.82–2.38), but was poor quality due to inadequate randomization and different follow-up lengths between the LDCT groups and the control group.

The US Preventive Services Task Force recommends annual screening with LDCT in adults aged 55 to 80 years with a 30 pack-year smoking history and currently smoking or have quit in the last 15 years.⁵ The task force recommends discontinuation of screening once the person has not smoked for 15 years or based on life expectancy. (B recommendation, high certainty that the net benefit is moderate, and the service should be offered.)

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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.

Are dietary modifications effective for preventing gout attacks?

Evidence-Based Answer
Increased coffee consumption is associated with reduced gout flares (SOR: \( B \), longitudinal study). Consumption of animal-based purines and, to a lesser extent, plant-based purines increases the risk of gout flares (SOR: \( B \), longitudinal study).

A 2007 longitudinal study recruited patients from a larger study of health professionals to observe the relation of coffee intake to the incidence of gout.\(^1\) Over 12 years, 45,869 men (age range 40–75 years) with no history of gout were followed every 4 years. A food-frequency questionnaire was used to gauge consumption of caffeinated coffee grouped into 5 categories (0, <1, 1–3, 4–5, and ≥6 cups per day) and decaffeinated coffee into 4 categories (0, <1, 1–3, and >4 cups per day).

Increasing coffee intake was associated with decreasing risk of developing gout. The relative risk for developing gout for the categories of increasing caffeinated coffee consumption compared with no coffee consumption were 0.97, 0.92, 0.60 (95% CI, 0.41–0.87), and 0.41 (95% CI, 0.19–0.88), respectively (\( P \) for trend=.009). For decaffeinated coffee consumption compared with no coffee consumption, the relative risks were 0.83, 0.67 (95% CI, 0.54–0.82), and 0.73 (95% CI, 0.46–1.17), respectively (\( P \) for trend=.002). There was no association between tea consumption and gout flares.\(^1\)

A 2012 longitudinal study recruited 633 adult US residents via Internet advertisement to determine the effect of purine consumption on gout for 1 year.\(^2\) Study eligibility requirements included a diagnosis of gout and a recent attack within the last 12 months. Purine intake was logged into a food questionnaire retrospectively for the 2 days prior to the gout flare and for 2-day control periods at 3, 6, 9, and 12 months.

The rate of gout attacks increased with increasing quintiles of purine intake. Compared with the lowest quintile of total purine intake, odds ratio for recurrent gout attacks were 1.17, 1.38, 2.21, and 4.76 with each increasing quintile (\( P \) for trend <.001). The rate of gout attacks was higher for purine intake from animal sources than from plants. The odds ratios of recurrent gout attacks from animal sources were 1.42, 1.34, 1.77, and 2.41, respectively, with increasing quintile (\( P \) for trend <.001) compared with 1.12, 0.99, 1.32, and 1.39 from plant sources (\( P \) for trend <.04).\(^2\)

A 2012 RCT examined the effect of consumption of skim milk powder enriched with GMP and G600 (products with known anti-inflammatory properties) on the frequency of gout flares.\(^3\) Adult patients (N=120) recruited from rheumatology clinics, who had a diagnosis of gout and experienced at least 2 gout flares within the past 4 months, were randomized into 3 groups: skim milk powder (SMP) enriched with GMP and G600, lactose powder control, and SMP control. The powders were mixed into a 250-mL vanilla shake and consumed daily for 3 months.

The GMP/G600 group exhibited approximately 1 less flare per month over 3 months compared with 0.5 to 0.75 fewer flares per month for the 2 control groups (\( P=.031 \)). However, there was no significant difference between SMP and the lactose control group in the frequency of gout flares.\(^3\)

Among healthy term infants, is delayed cord clamping superior to usual practice for preventing clinically significant anemia at 6 months of age?

Evidence-Based Answer
Delaying cord clamping (DCC) longer than 1 minute after delivery of the infant’s shoulders appears to increase hemoglobin levels at 24 to 48 hours, but increases the risk of phototherapy for jaundice (SOR: \( A \), meta-analysis of RCTs). Hemoglobin levels at 3 to 6 months do not significantly differ between infants in the early cord clamping (ECC) and DCC groups, but iron deficiency is twice as likely at 6 months of age in the ECC group (SOR: \( C \), meta-analysis of RCTs of disease-oriented outcomes).

A 2013 Cochrane review including 15 RCTs with a total of 3,911 women and infant pairs evaluated the effects of ECC versus DCC (range 1–5 minutes) on maternal
and neonatal outcomes. No significant difference was noted in hemoglobin levels between ECC and DCC at 3 to 6 months (5 trials, N=1,115; mean difference [MD] −0.15 g/dL; 95% CI, −0.48 to 0.19). Hemoglobin levels at 24 to 48 hours were significantly lower in the ECC group (4 trials, N=884; MD −1.5 g/dL; 95% CI, −1.8 to −1.2). Infants in the ECC group required less phototherapy for jaundice (7 trials, N=2,324; RR 0.62; 95% CI, 0.41–0.96). There was significantly reduced chance of being iron deficient for infants in the DCC group at 3 to 6 months postdelivery (5 trials, N=1,152; RR 2.7; 95% CI, 1.0–6.7). The review found high statistical heterogeneity in the analyses, secondary to variation with the way anemia was defined between trials. The authors recommend a more liberal timing to cord clamping as long as access to phototherapy for the increased risk of jaundice is available.

The World Health Organization (WHO) cites moderate-quality evidence and gives a strong recommendation for the use of DCC while initiating essential newborn care. They give an approximate time range for DCC of 1 to 3 minutes after birth, which applies to both vaginal and C-section births in term and preterm infants.

DCC remains neither recommended nor discouraged by the American Congress of Obstetricians and Gynecologists (ACOG). In a 2012 Committee Opinion, ACOG acknowledged evidence that supported DCC (defined as 30–60 seconds after birth with the infant below the level of the placenta) in preterm infants to reduce intraventricular hemorrhage, but called the available evidence insufficient to support DCC in term infants, especially in settings with “rich resources.”

In 2013, the American Academy of Pediatrics published a statement of endorsement for the ACOG committee opinion.

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compared with the standard therapy group (HR 0.59; 95% CI, 0.39–0.89). Serious adverse events secondary to antihypertensive therapy including hypotension, syncope, bradycardia, arrhythmia, hyperkalemia, angioedema, and renal failure occurred more frequently in the intensive therapy group (3.3% vs 1.3%; \( P < .001 \)).

A 2014 prospective cohort study examined the risk of CV events in 4,480 hypertensive patients without known coronary artery disease (CAD).\(^2\) Patients were allocated to 3 groups based on SBP response to treatment: elevated (≥140 mmHg), standard (120–139 mmHg), and low (<120 mmHg). The primary outcome measured was a composite of incident heart attack, CAD mortality, heart failure, and ischemic stroke. After 22 years of follow-up, there were 1,622 CV events.

The rate of CV events was significantly increased in the elevated SBP group compared with the low SBP group (HR 1.5; 95% CI, 1.3–1.7). There was no increase in CV events in the standard SBP group compared with the low SBP group (HR 1.0; 95% CI, 0.85–1.2).\(^3\)

The 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults, The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH), and the European Society of Cardiology (ESC) all found insufficient evidence from available RCTs to support a SBP goal of <130 mmHg, even in high-risk patients.\(^4,5\)

The recommendation, based on expert opinion, is a SBP goal of <140 mmHg.

### Are prophylactic antibiotics beneficial for preventing cellulitis in patients with a history of recurrent cellulitis?

**Evidence-Based Answer**
Prophylactic antibiotics decrease the risk of recurrence by 45% to 54% in patients with a history of recurrent cellulitis; however, the ideal antibiotic, method of administration, and duration of treatment are unclear (SOR: A, systematic review with meta-analysis). Once prophylactic antibiotics are stopped, the rate of recurrence rises again to baseline (SOR: B, RCT).

A 2014 systematic review and meta-analysis of 5 studies with 535 patients assessed whether prophylactic antibiotics decreased recurrence rates of cellulitis in patients with a history of cellulitis.\(^1\) Patients were at least 16 years of age and had at least 1 documented episode of cellulitis in the past. In all 5 trials, patients who received antibiotics were compared with patients who received a placebo or no antibiotics. The type of antibiotic, route of administration, and duration of therapy varied among the studies. Interventions included erythromycin 250 mg twice daily for 18 months, penicillin G 1.2 million units IM every 15 days for an unclear duration, penicillin VK 250 mg PO twice daily for 12 months, and phenoxymethylpenicillin 1 to 2 g PO twice daily for an unclear duration. Reported length of follow-up in 4 studies ranged from 12 to 36 months, and it was not reported in one study.

The number of recurrences of cellulitis significantly decreased in the antibiotic intervention groups compared with placebo (RR 0.46; 95% CI, 0.26–0.79).\(^1\)

A 2014 double-blind RCT examined the effectiveness of 12 months of twice-daily oral penicillin 250 mg versus placebo to prevent recurrent cellulitis in 274 patients with 2 or more episodes of cellulitis of the leg.\(^2\) Patients were followed for 36 months. The primary outcome was the number of patients who experienced a recurrence.

There was a 45% reduction in the risk of a repeat episode of cellulitis in the treatment group compared with the control group during the 12-month treatment phase (HR 0.55; 95% CI, 0.35–0.86). However, the protective effect was not sustained during the 24 month follow-up after stopping the prophylactic penicillin (HR 1.1; 95% CI, 0.61–1.9). No significant difference was noted between the groups for adverse events (\( P = .5 \)).\(^2\)

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In 2014, the Infectious Diseases Society of America (IDSA) released an updated practice guideline on the treatment of skin and soft tissue infections. The guideline recommended identifying and treating predisposing conditions that increase the risk of cellulitis, such as edema, obesity, eczema, venous insufficiency, and toe web infections. If treatment or control of these factors is unsuccessful, the guideline recommended considering prophylactic antibiotics in patients with 3 to 4 episodes of cellulitis a year.

Recommended antibiotics were oral penicillin or erythromycin twice daily for 4 to 52 weeks, or intramuscular penicillin every 2 to 4 weeks. The guidelines recommended the prophylactic antibiotics continue as long as predisposing factors persist. This IDSA guideline was evidence-driven but also used expert opinion.

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What is the best hypnotic in elderly patients?

Evidence-Based Answer
Benzodiazepines and “z-class” sedatives (zolpidem, zopiclone, and zaleplon) are the most efficacious sleeping medications in terms of sleep latency and increase total sleep time by approximately 30 minutes, but may cause more harm than benefit (SOR: A, meta-analysis of RCTs). However, there does not appear to be an increased mortality risk with their use (SOR: B, single cohort study). Ramelteon appears to be less beneficial, but with fewer reported side effects (SOR: A, systematic review of RCTs).

A 2005 meta-analysis compared the risks and benefits of any pharmacologic treatment for insomnia in people aged ≥60 with no other psychiatric disorders. Drugs included benzodiazepines, zopiclone, zolpidem, zaleplon, and placebo. Trials that compared any sedative with placebo reported significantly improved sleep quality (8 trials, n=719; effect size 0.14; 95% CI, 0.05–0.23) and a separate 8 trials (n=601) comparing benzodiazepines with placebo noted increased total sleep time by an average of 25 minutes (range 12.8–37.8 minutes; P=.001). (Note: an effect size of 0.2 is considered small, 0.6 moderate, and 1.2 large.) Six trials (n=44) showed decreased nighttime awakenings for all hypnotics studied, by an average of 0.63 episodes per night (range 0.48–0.77; P<.0001).

In this meta-analysis, benzodiazepines had a larger effect on sleep quality (7 studies, n=277; effect size 0.37; 95% CI, 0.01–0.73), total sleep time (8 trials, n=524; increased 34 minutes, range 16–53 minutes; P<.01) and nighttime awakenings (6 trials, n=296; decrease of 0.60 episodes; range 0.41–0.78 fewer episodes; P<.0001) than placebo. No difference was noted between benzodiazepines and benzodiazepine receptor agonists (zaleplon, zolpidem, zopiclone) in sleep quality (3 trials; n=339; effect size 0.04; 95% CI, −1.1 to 1.2). There was also no difference in sleep quality with zopiclone compared with placebo (2 trials, n=116; effect size 0.41; 95% CI, −0.76 to 1.6) (and limited data for zolpidem or zaleplon versus placebo). On the basis of 4 trials (n=1,072), the number needed to treat with a sedative to improve sleep quality was 13 (range 6.7–63) while 16 trials (n=2,220) reported the number needed to harm as 6 (range 4.7–7.1).

Most common side effects were headache, nightmares, and gastrointestinal symptoms. Adverse cognitive effects were more common with all sedatives verses placebo (10 trials, n=712; OR 4.8; 95% CI, 1.5–15). A limitation of the study was that the analysis did not analyze different benzodiazepines separately or take into account varying half-lives. The studies were also based on subjective reports by the participants.

A 2013 prospective cohort trial of 6,696 community-dwelling elderly patients studied the association between hypnotic use and mortality over a 12-year period. Median age of the patients was 73 years (range 65–95 years). At baseline, 22% of the patients (n=1,454) were taking at least 1 hypnotic and 3.9% (n=212) reported taking 2 or more.

After adjusting for potential confounding factors such as chronic disease, anxiety, and depressive symptomatology, no significant difference was noted in mortality between those who had used hypnotics and those who did not (HR 1.1; 95% CI, 0.92–1.2), with 1,307 deaths observed (20% of study population).
A 2012 systematic review examined ramelteon on sleep latency in adults with chronic insomnia (8 RCTs, N=822), which included 200 elderly patients in a subgroup analysis over a 2-night trial.³ No significant difference was found between ramelteon and placebo in sleep latency (2 trials, N=200; mean difference −8.6 min, 95% CI, −17 to 0.20). The analysis was limited by inadequate access to original data and the smaller number of elderly patients studied.

A 2007 RCT included 829 patients with an average age of 72 years, who were not included in the meta-analysis subgroup discussed above (due to issues with data availability).⁴ Patients were treated for 5 weeks with placebo, 4 mg ramelteon, or 8 mg ramelteon. Patients recorded information about the previous night’s sleep in a sleep diary.

Ramelteon at 8 mg was found to reduce sleep latency by 9 minutes (P<.00001) compared with placebo, without a significant increase in side effects. Of note, 128 patients (15%) prematurely discontinued the double-blind treatment due to multiple factors including lack of efficacy, protocol deviation, adverse events, or withdrawal of consent.⁴

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Spotlight on Pharmacy

What is the best management of heart failure patients with renal failure and volume overload unresponsive to loop diuretics?

Bottom line

Stepped pharmacologic therapy with escalating doses of IV loop diuretic and oral metolazone is as effective as ultrafiltration for weight loss, but with superior preservation of renal function (SOR: B, RCT). Oral metolazone and IV chlorothiazide have similar effects on urine output when added to IV furosemide therapy (SOR: B, cohort study). Longer-term use of oral metolazone with oral loop diuretics may result in weight loss, but with modest worsening of renal function (SOR: C, case series).

Evidence summary

A 2012 RCT compared ultrafiltration with stepped diuretic therapy in 188 hospitalized patients with a ≥0.3 mg/dL serum creatinine (Cr) increase from baseline and persistent volume overload due to acute decompensated heart failure.¹² The design of this study was reported in 1 article, while the results were reported in a second article. Patients with a baseline Cr >3.5 mg/dL were excluded from the study. Diuretic therapy was initiated and then titrated every 24 hours for a total of 96 hours (see FIGURE).

In the ultrafiltration arm, the Aquadex System 100® performed fluid removal at a rate of 200 mL/h over a median of 40 hours. At 96 hours, the ultrafiltration group had a significant mean increase in serum Cr compared with the pharmacologic group (+0.23 vs −0.04 mg/dL; P=.003), but there was no significant difference in mean weight loss (−5.7 kg in ultrafiltration group vs −5.5 kg in pharmacologic group, P=.58). The 60-day, estimated all-cause mortality was similar (17% with ultrafiltration vs 13% with diuretic therapy; P=.47). The ultrafiltration arm had a higher rate of serious adverse events, primarily kidney failure, bleeding complications, and intravenous catheter-related complications (72% vs 57%; P=.03).²
A 2015, nonrandomized, retrospective, cohort study compared the addition of oral metolazone (median daily dose 2.5 mg) or IV chlorothiazide (median daily dose 500, 750, and 1,000 mg on day 1, 2, and 3 respectively) to IV furosemide therapy over 72 hours. The study included 55 hospitalized adult patients (median age 70) with acute decompensated heart failure (median ejection fraction 33%) and renal insufficiency (Cr clearance 15–50 mL/min).

Median net urine output (urine output minus fluid intake) for oral metolazone versus IV chlorothiazide at 72 hours was 4,828 versus 3,779 mL (P=.16). Seventy-three percent of patients in the metolazone group versus 55% in the chlorothiazide group achieved the target of ≥3,000 mL net urine output at 72 hours (P=.17). Two patients in the metolazone group and 3 in the chlorothiazide group had worsened renal failure, defined as Cr increase of >0.5 mg/dL.

A 2005 case series of 21 outpatients with refractory heart failure and median serum Cr of 1.76 mg/dL examined the effects of metolazone added to loop diuretic therapy. Metolazone (2.5–5.0 mg) added to a median dose of 260 mg/d furosemide (or equivalent dose of bumetanide) resulted in a 2-kg loss of median weight from baseline (P<.01) and an increase in median serum Cr from 1.73 to 2.19 mg/dL (P<.01) over a median treatment period of 25.5 days.

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REFERENCES
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