ClinicalEvidence

Altitude sickness

Search date October 2009

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ABSTRACT

INTRODUCTION: Up to half of people who ascend to heights above 2500 m may develop acute mountain sickness, pulmonary oedema, or cerebral oedema, with the risk being greater at higher altitudes, and with faster rates of ascent. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent, and to treat, acute mountain sickness? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 17 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: acetazolamide, descent versus resting, dexamethasone, gingko biloba, and slow ascent.

QUESTIONS

INTERVENTIONS

Footnote

*Although we found no RCTs on the effects of these interventions, there is a general consensus that they are effective.

Key points

- Up to half of people who ascend to heights above 2500 m may develop acute mountain sickness, pulmonary oedema, or cerebral oedema, with the risk being greater at higher altitudes, and faster rates of ascent.

  Symptoms of acute mountain sickness include headache, weakness, fatigue, nausea, insomnia, and decreased appetite.

  It is generally thought that symptoms resolve over a few days if no further ascent is attempted, but little is known about the long-term prognosis.

- We found little good-quality research on the prevention or treatment of this condition. There is consensus that slow ascent reduces the risk of acute mountain sickness.

- Acetazolamide and dexamethasone reduce the risk of developing acute mountain sickness compared with placebo, although we don't know whether they are more or less effective than each other or than other prophylactic treatments.

  Acetazolamide causes polyuria and paraesthesia in a high proportion of people while, in some people, dexamethasone may cause depression after withdrawal of treatment.

- We don't know whether ginkgo biloba reduces the risk of acute mountain sickness compared with placebo, but it may be less effective than acetazolamide.

- Dexamethasone may reduce symptom scores in people with acute mountain sickness compared with placebo.

- We don't know whether acetazolamide is effective in the treatment of symptoms of acute mountain sickness.

- There is consensus that people who develop acute mountain sickness should descend if possible, but we don't know of any RCTs showing that this improves symptoms compared with resting at the same altitude.

Clinical context

DEFINITION

Altitude sickness (or high-altitude illness) includes acute mountain sickness, high-altitude pulmonary oedema, and high-altitude cerebral oedema. **Acute mountain sickness** typically occurs at altitudes greater than 2500 m (about 8000 feet), and is characterised by the development of some or all of the symptoms of headache, weakness, fatigue, listlessness, nausea, insomnia, and suppressed appetite. Symptoms may take days to develop or may occur within hours, depending on the rate of ascent and the altitude attained. More severe forms of altitude sickness have been identified. **High-altitude pulmonary oedema** is characterised by symptoms and signs typical of pulmonary oedema, such as shortness of breath, coughing, and production of frothy or blood-stained sputum. **High-altitude cerebral oedema** is characterised by confusion, ataxia, and a decreasing level of consciousness. This review covers only acute mountain sickness.

INCIDENCE/ PREVALENCE

The incidence of acute mountain sickness increases with absolute height attained and with the rate of ascent. One survey in Taiwan (93 people ascending above 3000 m) found that 27% of people experienced acute mountain sickness. [1] One survey in the Himalayas (278 unacclimatised hikers at 4243 m) found that 53% of people developed acute mountain sickness. [2] One survey in the Swiss Alps (466 climbers at 4 altitudes between 2850 m and 4559 m) found the prevalence of two or more symptoms of acute mountain sickness to be 9% of people at 2850 m, 13% of people at 3050 m, 34% of people at 3650 m, and 53% of people at 4559 m. [3]

AETIOLOGY/ RISK FACTORS

One survey in the Himalayas identified the rate of ascent and absolute height attained as the only risk factors for acute mountain sickness. [2] It found no evidence of a difference in risk between men and women, or that previous episodes of altitude experience, load carried, or recent respiratory infections, affected risk. However, the study was too small to exclude these as risk factors, or to quantify risks reliably. One systematic review (search date 1999) comparing prophylactic agents versus placebo found that, among people receiving placebo, the incidence of acute mountain sickness was higher with a faster rate of ascent (54% of people at a mean ascent rate of 91 m/hour; 73% at a mean ascent rate of 1268 m/hour; 89% at a simulated ascent rate in a hypobaric chamber of 1647 m/hour). [4] One survey in Switzerland (827 mountaineers ascending to 4559 m) examined the effects of susceptibility, pre-exposure, and ascent rate on acute mountain sickness. [5] In this study, pre-exposure was defined as having spent more than 4 days above 3000 m in the preceding 2 months, and slow ascent was defined as ascending in more than 3 days. It found that, in susceptible people (who had previously had acute mountain sickness at high altitude), the prevalence of acute mountain sickness was 58% with rapid ascent and no pre-exposure, 29% with pre-exposure only, 33% with slow ascent only, and 7% with both pre-exposure and slow ascent. [5] In non-susceptible people, the corresponding values were 31%, 16%, 11%, and 4%. The overall odds ratio for developing acute mountain sickness in susceptible compared with non-susceptible people was 2.9 (95% CI 2.1 to 4.1). [5]

PROGNOSIS

We found no reliable data on prognosis. It is widely held that if no further ascent is attempted, then the symptoms of acute mountain sickness tend to resolve over a few days. We found no reliable data about long-term sequelae in people whose symptoms have completely resolved.

AIMS OF INTERVENTION

To prevent acute mountain sickness; to achieve rapid resolution of acute mountain sickness, with minimal adverse effects.

OUTCOMES

Prevention: incidence and/or severity of acute mountain sickness, incidence of individual symptoms, adverse effects of treatment. **Treatment:** clinical resolution and/or severity of acute mountain sickness, resolution of individual symptoms, adverse effects of treatment.

METHODS

Clinical Evidence search and appraisal October 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to October 2009, Embase 1980 to October 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4. An additional search within the Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language. RCTs had to be at least single-blind for drug interventions, but open studies were acceptable for other options. RCTs had to contain 20 or more individuals of whom 80% or more were followed up. There was no minimum length of follow-up required to include studies. For drug studies, we excluded all studies described as "open", "open label", not blinded, or single-blinded. We excluded crossover trials that did not report pre-crossover results. We excluded RCTs if rates of ascent and absolute

altitude were different between treatment groups. We excluded individual RCTs that examined effects of simulated altitude in hypobaric chambers. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 11). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of interventions to prevent acute mountain sickness?

OPTION ACETAZOLAMIDE (PREVENTION)

Prevention of altitude sickness
Compared with placebo Acetazolamide (250–700 mg) is more effective at reducing the proportion of people who develop acute mountain sickness (moderate-quality evidence).

Compared with ginkgo biloba Acetazolamide seems more effective at reducing the proportion of people who develop altitude sickness (moderate-quality evidence).

Adverse effects: paraesthesia
Compared with placebo Acetazolamide is associated with higher rate of paraesthesia (moderate-quality evidence).

Compared with ginkgo biloba Acetazolamide seems to be associated with a higher rate of paraesthesia (moderate-quality evidence).

Note
We found no clinically important results from RCTs about the effects of acetazolamide compared with dexamethasone.

For GRADE evaluation of interventions for altitude sickness, see table, p 11 .

Benefits:

Acetazolamide versus placebo:
We found one systematic review [4] and five subsequent RCTs. [6] [7] [8] [9] [10] The systematic review (search date 1999) compared acetazolamide 500 or 750 mg daily versus placebo at altitudes above 4000 m. [4] It found that acetazolamide significantly increased the proportion of people who remained free of acute mountain sickness compared with placebo (9 RCTs, 295 people; 103/153 [67%] with acetazolamide *v* 59/142 [42%] with placebo; RR 1.58, 95% CI 1.27 to 1.96). One RCT (48 people) included in the meta-analysis used a hypobaric chamber to simulate altitude. [4]

The first subsequent RCT (197 trekkers in Nepal) compared acetazolamide 125 mg twice daily versus placebo at altitudes between 4243 m and 4937 m. [6] It found that acetazolamide significantly reduced the proportion of people with acute mountain sickness compared with placebo (9/74 [12%] with acetazolamide *v* 20/81 [25%] with placebo; P = 0.04).

The second subsequent RCT (614 trekkers in Nepal) compared four treatments at altitudes between 4280 m and 4928 m: ginkgo biloba 120 mg twice daily (157 people), acetazolamide 250 mg twice daily (152 people), ginkgo biloba 120 mg twice daily plus acetazolamide 250 mg twice daily (154 people), and placebo (151 people). [7] It found that acetazolamide significantly reduced the proportion of people with acute mountain sickness at 1 to 2 days compared with placebo (14/118 [12%] with acetazolamide *v* 40/119 [34%] with placebo; OR 0.27, 95% CI 0.14 to 0.52).

The third subsequent RCT (68 people in California) compared three treatments after rapid ascent to 3800 m: acetazolamide 250 mg twice daily (24 people), ginkgo biloba 120 mg twice daily (21 people), and placebo (23 people). [8] It found no significant difference between acetazolamide and placebo in the proportion of people who developed acute mountain sickness, although the rate was smaller with acetazolamide (6/20 [30%] with acetazolamide *v* 12/20 [60%] with placebo; ARR

+30%, 95% CI –15% to +61%). This RCT might have been underpowered to detect a clinically important difference between groups.

The fourth subsequent RCT (204 trekkers in Nepal) compared three treatments after ascent to 4928 m: acetazolamide 375 mg twice daily (78 people), acetazolamide 125 mg twice daily (67 people), and placebo (59 people). [9] It found that both acetazolamide regimens significantly reduced the proportion of people with acute mountain sickness compared with placebo (composite incidence of acute mountain sickness: 14/68 [21%] with acetazolamide 375 mg twice daily *v* 14/58 [24%] with acetazolamide 125 mg twice daily *v* 27/53 [51%] with placebo; 95% CI for differences: low-dose acetazolamide *v* placebo, 8% to 46%; higher-dose acetazolamide *v* placebo, 12% to 49%).

The fifth subsequent RCT (44 people in Colorado) compared acetazolamide 125 mg twice daily versus placebo after rapid ascent (rate of 2300 m in 2 hours) from 1600 m to 4300 m. [10] It found that acetazolamide significantly reduced the proportion of people with acute mountain sickness compared with placebo (diagnostic criteria: AMS-cerebral factor score [derived from Environmental Symptoms Questionnaire] 0.7 or greater together with Lake Louise Symptom questionnaire score 3 or greater plus headache; 3/22 [14%] with acetazolamide *v* 10/22 [45%] with placebo; P = 0.02).

Acetazolamide versus dexamethasone:
We found no systematic review or RCTs of sufficient quality.

Acetazolamide versus ginkgo biloba:
We found no systematic review but found two RCTs. [7] [8] The first RCT (614 trekkers in Nepal) compared four treatments at altitudes between 4280 m and 4928 m: ginkgo biloba 120 mg twice daily (157 people), acetazolamide 250 mg twice daily (152 people), ginkgo biloba 120 mg twice daily plus acetazolamide 250 mg twice daily (154 people), and placebo (151 people). [7] It found that acetazolamide reduced the proportion of people with acute mountain sickness compared with ginkgo biloba, but the significance of this reduction was not assessed (14/118 [12%] with acetazolamide *v* 43/124 [35%] with ginkgo biloba; significance not assessed).

The second RCT (68 people in California) compared three treatments after rapid ascent to 3800 m: acetazolamide 250 mg twice daily (24 people), ginkgo biloba 120 mg twice daily (21 people), and placebo (23 people). [8] It found that acetazolamide reduced the proportion of people who developed acute mountain sickness compared with ginkgo biloba, but the significance of this reduction was not assessed (6/20 [30%] with acetazolamide *v* 11/17 [65%] with ginkgo biloba; significance not assessed).

Harms:

Acetazolamide versus placebo:
The review found that polyuria and paraesthesia were significantly more common with acetazolamide compared with placebo (polyuria: 5 RCTs, 150 people: 26/78 [33%] with acetazolamide *v* 4/72 [6%] with placebo; RR 4.24, 95% CI 1.92 to 9.37; paraesthesia: 4 RCTs, 99 people: 21/49 [43%] with acetazolamide *v* 5/50 [10%] with placebo; RR 4.02, 95% CI 1.71 to 9.43). [4] It reported that the adverse effects with acetazolamide were of "minor severity": the term "minor" was not further defined.

The first subsequent RCT found that paraesthesia was significantly more common with acetazolamide compared with placebo (36/74 [49%] with acetazolamide *v* 3/81 [4%] with placebo; P less than 0.001). [6]

The second subsequent RCT also found that, compared with placebo, acetazolamide was associated with significant increases in paraesthesia, urinary frequency, and dysgeusia (paraesthesia: 85/118 [72%] with acetazolamide *v* 12/119 [10%] with placebo; OR 25.0, 95% CI 11.1 to 50.0; urinary frequency: 10/118 [8%] with acetazolamide *v* 2/119 [2%] with placebo; OR 5.6, 95% CI 1.2 to 25.0; dysgeusia: 13/118 [11%] with acetazolamide *v* 3/119 [3%] with placebo; OR 4.8, 95% CI 1.3 to 16.7). [7]

The third subsequent RCT found that the most common adverse effect associated with acetazolamide was paraesthesia (7/20 [35%] with acetazolamide *v* 0/20 [0%] with placebo; significance not assessed). [8]

The fourth subsequent RCT found that paraesthesia was more common with both doses of acetazolamide compared with placebo, and was significantly more common with the higher dose of acetazolamide compared with the lower dose (70/77 [91%] with acetazolamide 375 mg twice daily *v* 47/62 [76%] with acetazolamide 125 mg twice daily *v* 16/51 [31%] with placebo; significance of comparisons versus placebo not assessed; P = 0.02 for high *v* low dose of acetazolamide). [9]

The fifth subsequent RCT gave no information on adverse effects. [10]

Acetazolamide versus dexamethasone:
We found no RCTs.

Acetazolamide versus ginkgo biloba:
The first RCT found that, compared with ginkgo biloba, acetazolamide was associated with a higher rate of paraesthesia and urinary frequency (paraesthesia: 85/118 [72%] with acetazolamide *v* 10/124 [8%] with ginkgo biloba; urinary frequency: 10/118 [8%] with acetazolamide *v* 2/124 [2%] with ginkgo biloba; significance not assessed). [7]

The second RCT found that acetazolamide was associated with a higher rate of paraesthesia compared with ginkgo biloba, but a significance assessment was not performed (7/20 [35%] with acetazolamide *v* 0/17 [0%] with ginkgo biloba; significance not assessed). [8]

Comment: The two multi-arm RCTs described in this option also included comparisons of ginkgo biloba versus placebo and are reported under benefits of ginkgo biloba option for prevention of acute mountain sickness, p 6 . [7] [8] A comparison of the effects of higher- versus lower-dose acetazolamide will be included in a future update of this review in *Clinical Evidence*.

OPTION DEXAMETHASONE (PREVENTION)

Prevention of altitude sickness
Compared with placebo Dexamethasone may be more effective at reducing the proportion of people who develop acute mountain sickness (low-quality evidence).

Adverse effects
Adverse effects (including depression) may occur in one quarter of people after withdrawal of dexamethasone.

Note
We found no clinically important results from RCTs about the effects of dexamethasone compared with acetazolamide.

For GRADE evaluation of interventions for altitude sickness, see table, p 11 .

Benefits:

Dexamethasone versus placebo:
We found one systematic review, [4] two additional RCTs (reported in one publication), [11] and one subsequent RCT. [12] The systematic review (search date 1999) compared dexamethasone (8, 12, or 16 mg/day) versus placebo at altitudes above 4000 m. [4] It found that dexamethasone significantly increased the proportion of people free of acute mountain sickness compared with placebo (8 RCTs, 161 people; AR for freedom from acute mountain sickness: 62% with dexamethasone *v* 26% with placebo; RR 2.50, 95% CI 1.71 to 3.66). Two RCTs (75 people) included in the meta-analysis simulated altitude in a hypobaric chamber. [4]

The two additional RCTs were excluded from the review because they compared dexamethasone versus placebo at altitudes less than 4000 m. [11] Both RCTs were undertaken in health professionals aged 18 to 65 years, who normally lived at altitudes less than 450 m, and who were participating in continuing medical education programmes in the Rocky Mountains. The first additional RCT found that dexamethasone (4 mg every 6 hours for a total of 6 doses) significantly reduced the proportion of people with acute mountain sickness compared with placebo (73 people, altitude 2700 m; AR for acute mountain sickness: 3/38 [8%] with dexamethasone *v* 14/35 [40%] with placebo; ARR 32%, 95% CI 14% to 50%; RR 0.20, 95% CI 0.06 to 0.65). [11] The second additional RCT found no significant difference in the proportion of people with acute mountain sickness between dexamethasone (4 mg every 6 hours for a total of 6 doses) and placebo (50 people, altitude 2050 m; AR for acute mountain sickness: 5/25 [20%] with dexamethasone *v* 4/25 [16%] with placebo; ARI +4%, 95% CI –17% to +25%; RR 1.25, 95% CI 0.62 to 1.78). [11] In the RCT conducted at 2050 m, event rates were low in both groups, probably because of the relatively low altitude. [11] The study might therefore have lacked power to detect clinically important differences between dexamethasone and placebo. The subsequent RCT compared five different treatments (3 different dosages of prednisolone, dexamethasone 0.5 mg, and placebo). [12] Acute mountain sickness was assessed using a scoring system based on symptoms and clinical assessment. People in the RCT were air-lifted to an altitude of 3450 m. The RCT found that dexamethasone significantly reduced the mean acute mountain sickness score after 2 days compared with placebo (5-arm RCT; 50 men, aged 19–24 years, normally resident at sea level; difference in mean acute mountain sickness score: P less than 0.001, results presented graphically, further details not reported).

Dexamethasone versus acetazolamide:
See benefits of acetazolamide for prevention of acute mountain sickness, p 3 .

Dexamethasone versus ginkgo biloba:
We found no systematic review or RCTs.

Harms:

Dexamethasone versus placebo:
The review reported that adverse effects, mainly depression, occurred on withdrawal of dexamethasone. [4] It found that withdrawal of dexamethasone significantly increased the incidence of all adverse effects (including depression) compared with placebo (adverse reactions on withdrawal: 13/48 [27%] people with dexamethasone *v* 0/43 [0%] with placebo; RR 4.45, 95% CI 1.08 to 18.3). With regard to depression specifically, of the five RCTs that looked for adverse effects in weaning from dexamethasone, the review stated that, in three RCTs, no adverse effect was noted; in the fourth RCT 8/17 (47%) people with dexamethasone experienced depression compared with 0/8 (0%) people with placebo; in the fifth RCT 1/7 (14%) people with dexamethasone experienced depression compared with 0/8 (0%) people with placebo (statistical analysis not reported). [4] The severity of depression was not reported. [4]

Dexamethasone versus acetazolamide:
See harms of acetazolamide for prevention of acute mountain sickness, p 3 .

Dexamethasone versus ginkgo biloba:
We found no RCTs.

Comment: None.

OPTION SLOW ASCENT (OR ACCLIMATISATION)

Prevention of altitude sickness
Slow ascent compared with rapid ascent Slow ascent may be more effective at reducing the proportion of people who develop acute mountain sickness (very low-quality evidence).

For GRADE evaluation of interventions for altitude sickness, see table, p 11 .

Benefits: We found no systematic review, but found one quasi-randomised controlled trial (35 mountaineers). Randomisation was based on mountaineers' preference for two departure dates: when all spaces in one group had been filled, remaining mountaineers were allocated to the other group. [13] The trial compared ascent from 3730 m to 7546 m over 15 days (rapid ascent) versus over 19 days (slow ascent). It found that climbers following the slow-ascent protocol had significantly lower acute mountain sickness scores compared with those following the faster-ascent protocol (mean Environmental Symptoms Questionnaire cerebral factor symptom scores at various heights; 5533 m [33 people]: 0.06 at day 6 of slow ascent *v* 0.17 at day 5 of rapid ascent; at 6265 m [29 people]: 0.26 at day 16 of slow ascent *v* 0.43 at day 12 of rapid ascent; 6865 m [26 people]: 0.41 at day 18 of slow ascent *v* 0.49 at day 19 of rapid ascent; 7546 m [summit; 17 people]: 0.53 at day of 19 of slow ascent *v* 0.69 at day 20 of rapid ascent; P less than 0.008; P value reported is for overall effect of altitude on AMS-cerebral factor score [derived from Environmental Symptoms Questionnaire]; significance of between-group differences at each height not assessed). The RCT reported that adjustments were made to the rapid-ascent protocol due to bad weather: on day 14, the group had to return to base camp at 4497 m. However, after 3 days' rest, the rapid-ascent group completed the ascent to the summit within 4 days (days 17–20) compared with within 6 days by the slow-ascent group (days 14–19).

Harms: The RCT gave no information on adverse effects. [13]

Comment: We also found one non-randomised controlled trial (60 male soldiers without previous high-altitude exposure) comparing faster versus slower ascent to an altitude of 3500 m. [14] Faster ascent was achieved by flying people to the target altitude (ascent time 1 hour) and slower ascent by driving them (ascent time 4 days). The trial found that slower ascent reduced the risk of any symptom of acute mountain sickness compared with faster ascent (AR for "1 symptom or another": 51% with slower ascent *v* 84% with faster ascent; P value not reported). Observational data suggest that faster ascent is a risk factor for acute mountain sickness (see aetiology/risk factors). [4]

Clinical guide:
Slow ascent is, in itself, unlikely to be harmful. Consensus suggests that slower ascent helps to prevent acute mountain sickness.

OPTION GINKGO BILOBA

Prevention of altitude sickness

Compared with placebo We don't know whether ginkgo biloba is more effective at reducing the proportion of people who develop altitude sickness (low-quality evidence).

Compared with acetazolamide Ginkgo biloba seems less effective at reducing the proportion of people who develop altitude sickness (moderate-quality evidence).

Adverse effects: paraesthesia
Compared with acetazolamide Gingko biloba seems to be associated with a lower rate of paraesthesia (moderate-quality evidence).

Note
We found no clinically important results from RCTs about the effects of ginkgo biloba compared with dexamethasone.

For GRADE evaluation of interventions for altitude sickness, see table, p 11 .

Benefits:

Ginkgo biloba versus placebo:
We found one systematic review (search date not reported; 7 RCTs, 715 people) assessing the effects of gingko biloba (variable doses and preparations) in preventing acute mountain sickness. [15] The review did not pool data and so we report data from identified RCTs that meet *Clinical Evidence* reporting criteria: one RCT identified by the review did not meet *Clinical Evidence* reporting criteria (open-label design) and is not discussed further. [16]

The first RCT (26 people in Hawaii) identified by the review compared ginkgo biloba 60 mg three times daily versus placebo during ascent from sea level to 4204 m over 3 hours. [17] It found that ginkgo biloba significantly reduced the proportion of people with severe acute mountain sickness compared with placebo (severe acute mountain sickness: 2/12 [17%] with ginkgo biloba *v* 9/14 [64%] with placebo; P = 0.021). However, there was no significant difference between groups in overall rate of acute mountain sickness (acute mountain sickness: 7/12 [58%] with ginkgo biloba *v* 13/14 [93%] with placebo; P = 0.07).

The second RCT (44 trekkers in Nepal) identified by the review compared ginkgo biloba extract (EGb 761) 160 mg twice daily versus placebo during ascent to over 5000 m over more than 7 days. [18] It found that, compared with placebo, ginkgo biloba significantly reduced the proportion of people with acute mountain sickness as assessed by two diagnostic criteria (diagnostic criteria: Environmental Symptoms Questionnaire cerebral factor [AMS-C] score greater than 0.7 or respiratory factor score greater than 0.6; cerebral factor: 0/22 [0%] with ginkgo biloba *v* 9/22 [41%] with placebo; P = 0.0014; respiratory factor: 3/22 [14%] with ginkgo biloba *v* 18/22 [82%] with placebo; P less than 0.0001).

The third RCT (614 trekkers in Nepal) identified by the review compared four treatments at altitudes between 4280 m and 4928 m: ginkgo biloba 120 mg twice daily (157 people), acetazolamide 250 mg twice daily (152 people), ginkgo biloba 120 mg twice daily plus acetazolamide 250 mg twice daily (154 people), and placebo (151 people). [7] It found no significant difference in the proportion of people with acute mountain sickness between ginkgo biloba alone and placebo (43/124 [35%] with ginkgo biloba *v* 40/119 [34%] with placebo; OR 1.05, 95% CI 0.62 to 1.79).

The fourth RCT (68 people in California) compared three treatments after rapid ascent to 3800 m: acetazolamide 250 mg twice daily (24 people), ginkgo biloba 120 mg twice daily (21 people), and placebo (23 people). [8] It found no significant difference in the proportion of people with acute mountain sickness between ginkgo biloba and placebo (11/17 [65%] with ginkgo biloba *v* 12/20 [60%] with placebo; ARI –5%, 95% CI –37% to +28%).

The fifth (40 people in Colorado) and sixth (44 people in Colorado) RCTs were reported in one publication. [19] The RCTs assessed the effects of two preparations of gingko biloba (both administered orally at a dose of 120 mg twice daily) versus placebo in people ascending from 2000 m to 4300 m over 2 hours. Gingko biloba or placebo were self-administered for either 4 days (fifth RCT) or 3 days (sixth RCT) before ascent to 4300 m and during the 24 hours spent at 4300 m. The fifth RCT found that, compared with placebo, ginkgo biloba significantly reduced the proportion of people who developed acute mountain sickness at 24 hours after ascent (diagnostic criteria: AMS-C score 0.7 or greater and Lake Louise score 3 or greater with headache: 7/21 [33%] with ginkgo biloba *v* 13/19 [68%] with placebo; P = 0.027). However, the sixth RCT found no significant difference between groups in the proportion of people with acute mountain sickness at 24 hours after ascent (4/15 [27%] with ginkgo biloba *v* 10/22 [45%] with placebo; P = 0.247). The RCTs were underpowered to detect a statistically significant difference between groups. The authors of the RCT reported that the key difference between the RCTs was the source of gingko biloba.

Ginkgo biloba versus acetazolamide:
See benefits of acetazolamide for prevention of acute mountain sickness, p 3 .

Ginkgo biloba versus dexamethasone:
See benefits of dexamethasone for prevention of acute mountain sickness, p 5 .

Harms:

Ginkgo biloba versus placebo:
The review gave no comparative data on adverse effects. [15]

The first RCT identified by the review found a similar incidence of severe headache with ginkgo biloba and placebo, whereas nausea was more common with placebo (severe headache: 1/12 [8%] with ginkgo biloba *v* 1/14 [7%] with placebo; nausea: 2/12 [17%] with ginkgo biloba *v* 4/14 [29%] with placebo; significance not assessed). [17] The second RCT gave no information on adverse effects. [18] The third RCT identified by the review found no significant difference between ginkgo biloba and placebo in paraesthesia or dysgeusia (paraesthesia: 10/124 [8%] with ginkgo biloba *v* 12/119 [10%] with placebo; OR 0.78, 95% CI 0.32 to 1.89; dysgeusia: 6/124 [5%] with ginkgo biloba *v* 3/119 [3%] with placebo; OR 1.96, 95% CI 0.48 to 8.33). [7] The fourth RCT identified by the review reported a similar incidence of adverse effects with ginkgo biloba and with placebo (dry mouth: 2/17 [12%] with ginkgo biloba *v* 4/20 [20%] with placebo; heart racing: 4/17 [24%] with ginkgo biloba *v* 4/20 [20%] with placebo; drowsiness: 4/17 [24%] with ginkgo biloba *v* 4/20 [20%] with placebo; increased urination: 3/17 [18%] with ginkgo biloba *v* 7/20 [35%] with placebo; significance not assessed). [8] The fifth and sixth RCTs (reported in one publication) identified by the review gave no information on adverse effects. [19]

Ginkgo biloba versus acetazolamide:
See harms of acetazolamide for prevention of acute mountain sickness, p 3 .

Ginkgo biloba versus dexamethasone:
See harms of dexamethasone for prevention of acute mountain sickness, p 5 .

Comment:
RCTs have found variable results on the effectiveness of gingko biloba in preventing acute mountain sickness. The systematic review found no reason for the disparate findings from RCTs, but recommended investigating the roles of specific active components of the different gingko biloba preparations used in the various studies. [15]

QUESTION What are the effects of treatments for acute mountain sickness?

OPTION DESCENT COMPARED WITH RESTING AT THE SAME ALTITUDE

We found no clinically important results from RCTs in people with acute mountain sickness about the effects of descent compared with resting at the same altitude. We found no clinically important results from RCTs about the effects of different distances of descent, or about the balance of risks and benefits, in people who might find it difficult to descend.

For GRADE evaluation of interventions for altitude sickness, see table, p 11 .

Benefits:
We found no systematic review or RCTs.

Harms:
We found no RCTs.

Comment:

Clinical guide:
Consensus suggests that people with acute mountain sickness should descend if possible. However, we found no RCTs examining the effects of different distances of descent, or about the balance of risks and benefits in people who might find it difficult to descend (e.g., owing to symptoms of acute mountain sickness or unrelated injury).

OPTION DEXAMETHASONE (TREATMENT)

Symptom severity
Compared with placebo Dexamethasone seems more effective at reducing mean acute mountain sickness symptom scores (moderate-quality evidence).

For GRADE evaluation of interventions for altitude sickness, see table, p 11 .

Benefits:
We found no systematic review. We found one RCT comparing dexamethasone (8 mg initially, then 4 mg after 6 and 12 hours) versus placebo without concurrent descent in either group. [20]

Acute mountain sickness was assessed using a scoring system based on symptoms and clinical assessment (score 0–14, where 14 was the most severe). The RCT found that, after treatment for 12 hours at the same altitude, dexamethasone improved mean symptoms scores significantly more than placebo (35 climbers arriving at an alpine hut with symptoms of acute mountain sickness, at an altitude of 4559 m; mean symptom score: 4.1 with dexamethasone *v* 0.4 with placebo; difference between groups 3.7, 95% CI 2.2 to 5.3). [20]

Harms: The RCT gave no information on adverse effects. [20] See harms of dexamethasone for prevention of acute mountain sickness, p 5 .

Comment: None.

OPTION ACETAZOLAMIDE (TREATMENT)

We found no direct information from RCTs about the effects of acetazolamide in the treatment of altitude sickness.

For GRADE evaluation of interventions for altitude sickness, see table, p 11 .

Benefits: We found no systematic review or RCTs of sufficient quality (see comment below).

Harms: We found no RCTs of sufficient quality (see comment below). See harms of acetazolamide in prevention of acute mountain sickness, p 3 .

Comment: We found one small RCT (12 climbers in Alaska with established acute mountain sickness, at an altitude of 4200 m) comparing acetazolamide versus placebo, which did not meet *Clinical Evidence* criteria for inclusion in the benefits section (at least 10 people per treatment arm). [21] Acute mountain sickness was assessed using a recognised symptom scoring system (defined as a score of 2 or greater on a symptom severity scale of 1–3, where 3 was the most severe). One person was assigned (non-randomly) to placebo because of drug allergy. The RCT found that acetazolamide significantly improved symptoms of acute mountain sickness after 24 hours compared with placebo (1/6 [17%] with acetazolamide *v* 6/6 [100%] with placebo; P = 0.015). The RCT stated that "no significant side effects of acetazolamide were reported".

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Acetazolamide for prevention One RCT added found that acetazolamide reduced the proportion of people who developed acute mountain sickness compared with placebo after rapid ascent from 1600 m to 4300 m. [10] Categorisation unchanged (Beneficial).

Ginkgo biloba for prevention One systematic review [15] added identified two RCTs (reported in one publication) [19] meeting *Clinical Evidence* reporting criteria. The RCTs assessed the effects of two preparations of gingko biloba versus placebo for prevention of acute mountain sickness. The RCTs, which were of similar size, found different results. One RCT found that, compared with placebo, gingko biloba reduced the proportion of people who developed acute mountain sickness, whereas the second RCT found no significant difference between groups for the same outcome. Categorisation unchanged (Unknown effectiveness).

Slow ascent (or acclimatisation) for prevention One small quasi-RCT added comparing ascent from 3730 m to 7546 m over 15 days (rapid ascent) versus over 19 days (slow ascent) found that climbers following the slow-ascent protocol had lower acute mountain sickness scores compared with those following the faster-ascent protocol. [13] However, the RCT had methodological flaws (low follow-up at some assessments, and variations in protocol). Evidence reassessed at update. Categorisation changed to Likely to be beneficial by consensus (previously Beneficial by consensus).

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Competing interests: DM declares that he has no competing interests.
We would like to acknowledge the previous contributors of this review, including Bazian Ltd.

Disclaimer

TABLE **GRADE evaluation of interventions for altitude sickness.**

Important outcomes			Prevention of altitude sickness, symptom severity, adverse effects						
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions to prevent acute mountain sickness?									
14 (954) [4] [6] [7] [8] [9] [10]	Prevention of altitude sickness	Acetazolamide *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for variation in dose of acetazolamide assessed
8 (721) [4] [6] [7] [8] [9]	Paraesthesia (adverse effect)	Acetazolamide *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for variation in dose of acetazolamide assessed
2 (279) [7] [8]	Prevention of altitude sickness	Acetazolamide *v* ginkgo biloba	4	–1	0	0	0	Moderate	Quality point deducted for not carrying out statistical assessment between groups
2 (279) [7] [8]	Paraesthesia (adverse effect)	Acetazolamide *v* ginkgo biloba	4	–1	0	0	0	Moderate	Quality point deducted for not carrying out statistical assessment between groups
11 (334) [4] [11] [12]	Prevention of altitude sickness	Dexamethasone *v* placebo	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for different study conditions
1 (33) [13]	Prevention of altitude sickness	Slow ascent *v* rapid ascent	4	–3	0	0	0	Very low	Quality points deducted sparse data, variations in study protocol, and not carrying out between group statistical assessments for all heights
6 (427) [7] [8] [17] [18] [19]	Prevention of altitude sickness	Ginkgo biloba *v* placebo	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for different regimens used
What are the effects of treatments for acute mountain sickness?									
1 (35) [20]	Symptom severity	Dexamethasone *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes.