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Interventions for preventing high altitude illness: Part 2. Less commonly-used drugs (Review)

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[Intervention Review]

Interventions for preventing high altitude illness: Part 2. Less commonly-used drugs

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ABSTRACT

Background

High altitude illness (HAI) is a term used to describe a group of mainly cerebral and pulmonary syndromes that can occur during travel to elevations above 2500 metres (~ 8200 feet). Acute mountain sickness (AMS), high altitude cerebral oedema (HACE) and high altitude pulmonary oedema (HAPE) are reported as potential medical problems associated with high altitude ascent. In this second review, in a series of three about preventive strategies for HAI, we assessed the effectiveness of five of the less commonly used classes of pharmacological interventions.

Objectives

To assess the clinical effectiveness and adverse events of five of the less commonly used pharmacological interventions for preventing acute HAI in participants who are at risk of developing high altitude illness in any setting.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) in May 2017. We adapted the MEDLINE strategy for searching the other databases. We used a combination of thesaurus-based and free-text search terms. We scanned the reference lists and citations of included trials and any relevant systematic reviews that we identified for further references to additional trials.

Selection criteria

We included randomized controlled trials conducted in any setting where one of five classes of drugs was employed to prevent acute HAI: selective 5-hydroxytryptamine(1) receptor agonists; N-methyl-D-aspartate (NMDA) antagonist; endothelin-1 antagonist; anticonvulsant drugs; and spironolactone. We included trials involving participants who are at risk of developing high altitude illness

(AMS or HACE, or HAPE, or both). We included participants with and without a history of high altitude illness. We applied no age or gender restrictions. We included trials where the relevant medication was administered before the beginning of ascent. We excluded trials using these drugs during ascent or after ascent.

Data collection and analysis

We used the standard methodological procedures employed by Cochrane.

Main results

We included eight studies (334 participants, 9 references) in this review. Twelve studies are ongoing and will be considered in future versions of this review as appropriate. We have been unable to obtain full-text versions of a further 12 studies and have designated them as 'awaiting classification'. Four studies were at a low risk of bias for randomization; two at a low risk of bias for allocation concealment. Four studies were at a low risk of bias for blinding of participants and personnel. We considered three studies at a low risk of bias for blinding of outcome assessors. We considered most studies at a high risk of selective reporting bias.

We report results for the following four main comparisons.

Sumatriptan versus placebo (1 parallel study; 102 participants)

Data on sumatriptan showed a reduction of the risk of AMS when compared with a placebo (risk ratio (RR) = 0.43, CI 95% 0.21 to 0.84; 1 study, 102 participants; low quality of evidence). The one included study did not report events of HAPE, HACE or adverse events related to administrations of sumatriptan.

Magnesium citrate versus placebo (1 parallel study; 70 participants)

The estimated RR for AMS, comparing magnesium citrate tablets versus placebo, was 1.09 (95% CI 0.55 to 2.13; 1 study; 70 participants; low quality of evidence). In addition, the estimated RR for loose stools was 3.25 (95% CI 1.17 to 8.99; 1 study; 70 participants; low quality of evidence). The one included study did not report events of HAPE or HACE.

Spironolactone versus placebo (2 parallel studies; 205 participants)

Pooled estimation of RR for AMS was not performed due to considerable heterogeneity between the included studies (I^2 = 72%). RR from individual studies was 0.40 (95% CI 0.12 to 1.31) and 1.44 (95% CI 0.79 to 2.01; very low quality of evidence). No events of HAPE or HACE were reported. Adverse events were not evaluated.

Acetazolamide versus spironolactone (1 parallel study; 232 participants)

Data on acetazolamide compared with spironolactone showed a reduction of the risk of AMS with the administration of acetazolamide (RR = 0.36, 95% CI 0.18 to 0.70; 232 participants; low quality of evidence). No events of HAPE or HACE were reported. Adverse events were not evaluated.

Authors' conclusions

This Cochrane Review is the second in a series of three providing relevant information to clinicians and other interested parties on how to prevent high altitude illness. The assessment of five of the less commonly used classes of drugs suggests that there is a scarcity of evidence related to these interventions. Clinical benefits and harms related to potential interventions such as sumatriptan are still unclear. Overall, the evidence is limited due to the low number of studies identified (for most of the comparison only one study was identified); limitations in the quality of the evidence (moderate to low); and the number of studies pending classification (24 studies awaiting classification or ongoing). We lack the large and methodologically sound studies required to establish or refute the efficacy and safety of most of the pharmacological agents evaluated in this review.

PLAIN LANGUAGE SUMMARY

Medicines less commonly used for preventing high altitude illness

Background

High altitude illness (HAI) is a term used to describe a group of brain and lung conditions that can occur during travel to altitudes above 2500 metres (~ 8200 feet). HAI-related conditions are generally characterized by headache, nausea, vomiting and tiredness (often called

acute mountain sickness), but primarily affect the brain (drowsiness, confusion or unconsciousness) or the lungs (cough, breathlessness) in different individuals. We assessed five classes of medicines less commonly used to prevent the onset of this illness in this review.

Study characteristics

The evidence is current to May 2017. We included eight studies and 334 participants related to five different classes of medicines sometimes recommended for HAI prevention. These medicines included those that mimic the action of serotonin at selected sites (selective 5-hydroxytryptamine(1) receptor agonists), medicines that regulate the action of calcium (N-methyl-D-aspartate (NMDA) antagonist), medicines that promote dilation of the blood vessels (endothelin-1 antagonist), medicines that prevent a neuron (nerve cell) from 'firing' (initiating an action) and convulsions from developing (anticonvulsant medicines), as well as medicines that regulate the body′ s sodium and water levels (spironolactone). All studies were undertaken in high altitude mountain areas. The participants ranged between 16 and 65 years of age. Only one study included people at a high risk of this condition due to their history of HAI. Four trials provided the intervention between one to three days prior to the ascent (50%), and three trials less than 24 hours prior (37.5%). The participants in all these studies reached a final altitude of between 3500 and 5895 metres above sea level. Only one of the eight included studies did not provide clear information about the source of funding (12.5%). Twenty-four additional studies were classified as ongoing (12), or awaiting classification (12; unable to obtain full texts).

Key results

The assessment of the less commonly used pharmacological interventions suggest that there is a scarcity of evidence related to these interventions. For most of the assessed comparisons, we only found evidence from a single study. Clinical benefits and harms related to potential interventions such as sumatriptan are still unclear.

Quality of the evidence

The quality of the evidence was rated from low to very low. Several studies had quality shortcomings such as only having small sample sizes and therefore generating uncertain results. For most of the medicines evaluated, additional research is required to clarify their effectiveness and safety.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Sumatriptan compared with placebo for preventing high altitude illness

Patient or population: participants at risk of high altitude illness
Setting: High altitude (Ecuador)
Intervention: sumatriptan
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Sumatriptan				
Risk of acute mountain sickness	**412 per 1000**	**177 per 1000** (91 to 346)	**RR 0.43** (0.21 to 0.84)	102 (1 study)	⊕⊕◯◯ **Low**[1]	
Risk of high altitude pulmonary oedema - not reported	Not estimable	Not estimable	Not estimable			Not reported
Risk of high altitude cerebral oedema - not reported	Not estimable	Not estimable	Not estimable			Not reported
Risk of adverse events - not reported	Not estimable	Not estimable	Not estimable			Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: we are very uncertain about the estimate.

[1] Downgraded 2 levels due to imprecision.

BACKGROUND

High altitude illness (HAI) is a term used to describe a group of cerebral and pulmonary syndromes that can occur during travel to elevations above 2500 metres (m) (~ 8200 feet). HAI is commonly classified as high (1500 m to 3500 m), very high (above 3500 m to 5500 m) and extreme (above 5500 m) (Flaherty 2016; Kayser 2012; Khodaee 2016; Low 2012; Paralikar 2010; Zafren 2014). Because of the large number of people who ascend rapidly to between 2500 m and 3500 m, high altitude illness is common in this height range as a result of hypoxia (Davis 2017; Paralikar 2010). Although the proportion of oxygen remains unchanged at 20.93%, increases in altitude result in a lower partial pressure of oxygen in the inspired air (Anonymous 1892; Wilson 2009). This reduction in the driving pressure of oxygen along the oxygen cascade from the lungs to the tissues can compromise the supply of oxygen to the tissues (Wilson 2009), especially the cardiovascular and pulmonary systems (Leissner 2009). The physiological responses to hypoxia and acclimatization related to HAI include hyperventilation (increased depth and rate of breathing); elevation of systemic blood pressure; and tachycardia (elevations of heart rate) (Leissner 2009; Naeije 2010). However, in many instances these physiological changes may be inadequate, so that the ascent to high altitude and the attendant hypoxia are complicated by altitude-associated medical illness (Luks 2017; Palmer 2010), which is also known as high altitude illness (HAI).

Description of the condition

High altitude illness (HAI)

As mentioned earlier, HAI is a term used to describe a group of mainly cerebral and pulmonary syndromes that can occur during travel to elevations above 2500 metres. There are two types of mountain sickness: acute mountain sickness; and chronic mountain sickness (CMS), also called Monge's disease (Monge 1942). Acute hypoxia, acute mountain sickness (AMS), high altitude cerebral oedema (HACE), high altitude pulmonary oedema (HAPE), cerebrovascular syndromes, peripheral oedema, retinopathy, thromboembolism, sleep disorders and periodic breathing, high altitude pharyngitis and bronchitis, ultraviolet exposure and keratitis (snow blindness), and exacerbation of pre-existing illness are reported as potential medical problems associated with high altitude ascent (CATMAT 2007; Kayser 2012; Khodaee 2016; Palmer 2010; Schoene 2008). Factors such as the rate of ascent, the absolute change in altitude, and individual physiology are factors usually implicated in the development of these conditions (Flaherty 2016; Leissner 2009; Low 2012; Luks 2017; Palmer 2010; Zafren 2014). The risk categories for acute mountain sickness are shown in Appendix 1 (Luks 2010).

In the 19th century Dr Daniel Vergara, a Mexican physiologist, pioneered studies on high altitude physiology and the physiological and anatomical mechanisms of adaptation to high elevations. Forty years later Dr Carlos Monge, a Peruvian physiologist, reported his ideas on this issue. The work of these pioneers was summarized early this century (Rodríguez de Romo 2002). Both the physiology and pathophysiology of high altitude have recently been widely reviewed (Bärtsch 2007; Davis 2017; Leissner 2009; Luks 2017; Palmer 2010; Paralikar 2010). In brief, these reviews confirm both the increase in respiratory rate and increase in haemoglobin concentration on exposure to low oxygen pressure. They identify the rate of ascent, the absolute change in altitude and individual variation in physiology as the primary determinants of whether HAI will develop or not (Palmer 2010). In addition, HAI is considered an important cause of mountain mortality (Windsor 2009).

Acute mountain sickness (AMS) or high altitude cerebral oedema (HACE)

AMS is a disorder with prominent neurological features, characterized by headache, anorexia, nausea and sometimes vomiting, light-headedness, insomnia, and fatigue (Bailey 2009; Leissner 2009; Palmer 2010). Headache is the most prevalent symptom of acute mountain sickness. In contrast, HACE is a potentially fatal neurological disorder and it is characterized by altered consciousness or ataxia (Bailey 2009; Hackett 2004; Imray 2010), or both, in an individual with AMS. If left untreated, HACE can result in death due to cerebral oedema (Bailey 2009). HACE is widely viewed as the end stage of AMS and is normally preceded by symptoms of AMS, which suggest a similar pathophysiological process (Bailey 2009; Imray 2010; Palmer 2010). It has been suggested that both syndromes could share a common pathophysiology linked by intracranial hypertension (Bailey 2009; Davis 2017; Kallenberg 2007; Luks 2017; Mairer 2012; Schoonman 2008; Wilson 2009). The severity of AMS can be scored using questionnaires such as the Lake Louise Questionnaire, Environmental Symptoms Questionnaire, or by the use of a simple analogue scale (Imray 2010). Headache is a very common symptom at altitude and some authors have suggested it could be viewed as a distinct clinical entity.

The definition of AMS seems to be problematic, as it will vary greatly between studies. A Lake Louise Score greater than 2 (including headache) is not equivalent to a criterion score of 0.70 with AMS-C (cerebral) from the Environmental Symptoms Questionnaire (Maggiorini 1998). The value of the AMS-R score is questionable for diagnosing AMS (Dumont 2000). Pathophysiology with a focus on the molecular basis of AMS and HACE has been widely described by Bailey 2009; and advances in the genetics, molecular mechanisms, and physiology that underpin them have been extensively described by Wilson 2009. This review will treat headache as a common and early symptom of AMS. Indeed, the exact definition of what constitutes AMS will vary when using different scoring systems and when interpreted by different authors.

High altitude pulmonary oedema (HAPE)

HAPE is a non-cardiogenic pulmonary oedema (Luks 2008a; Schoene 2004; Stream 2008). It is characterized by cough, progressive dyspnoea with exertion, and decreased exercise tolerance, generally developing within two to four days after arrival at high altitude (Palmer 2010; Stream 2008). It is rare after one week of acclimatization at a particular altitude (Maggiorini 2010; Palmer 2010). Hypoxia is the trigger that results in a complex cascade of events leading to HAPE (Stream 2008). Essentially, HAPE is due to a "persistent imbalance between the forces that drive water into the airspace and the biologic mechanisms for its removal" (Scherrer 2010); and the hallmark of this condition is hypoxic pulmonary hypertension. The hypertension may be mediated via at least four potential mechanisms: defective pulmonary nitric oxide synthesis; exaggerated endothelin-1 synthesis; exaggerated sympathetic activation; and a defect in alveolar transepithelial sodium transport (Scherrer 2010). An extensive review of pulmonary hypertension induced by HAI is reported by Pasha 2010.

Epidemiology of acute HAI

It has been estimated that 84% of people who fly directly to 3860 m are affected by AMS (Murdoch 1995). The risk of HACE and HAPE is much lower than for AMS, with estimates in the range of 0.1% to 4.0% (Basnyat 2003). The rate of ascent, altitude reached (especially the sleeping altitude), and individual susceptibility have been proposed as the most important risk factors for the development of HAI conditions (Basnyat 2003; Schneider 2002). Other presumptive risk factors are history of HAI and permanent residence lower than 900 m, exertion in children and adults (Basnyat 2003), obesity (Ri-Li 2003), and coronary heart disease (Dehnert 2010). It is advisable that those with asthma make sure that their condition is well controlled before they undertake exertion at altitude (CATMAT 2007).

See Appendix 2 for other medical terms.

Description of the intervention

The risk of high altitude illness (HAI) begins with a non-acclimatized subject ascending to an altitude higher than 2500 metres (Flaherty 2016; Kayser 2012; Khodaee 2016; Low 2012; Paralikar 2010). However, a susceptible individual may develop acute mountain sickness (AMS) at intermediate altitude such as 2100 metres (Davis 2017). Several interventions to prevent HAI conditions, especially AMS, have been described, compiled, and published in guidelines and consensus statements (CATMAT 2007; Flaherty 2016; Kayser 2012; Khodaee 2016; Low 2012; Luks 2010; Ritchie 2012; Seupaul 2012; Zafren 2014). Interventions for HAI prevention can be classified as pharmacological and non-pharmacological (Bärtsch 1992; Luks 2010; Luks 2008b; Wright 2008). The Committee to Advise on Tropical Medicine and Travel proposed a consensus for HAI in 2007, describing prevention and treatment approaches among several topics regarding this medical condition (CATMAT 2007).

In 2014 the Wilderness Medical Society (WMS) published an update of their 2010 guidelines, detailing prevention and treatment directives for HAI (AMS, HACE, HAPE) (Luks 2010; Luks 2014). This guideline was developed by an expert panel that compiled and classified all available evidence on HAI prevention and treatment. Recommendations, based on evidence using the American College of Chest Physicians' strategies, were agreed upon. For AMS and HACE, the experts proposed a risk classification where low-risk participants are discarded for prevention interventions; for HAPE, pharmacological prophylaxis is recommended for participants with a previous diagnosis of HAI (Luks 2014).

These previous reviews have not given a clear indication as to which preventative strategies (whether pharmacological or non-pharmacological) are of most use, nor how one might modify the approach in different situations. For example, while CATMAT 2007 suggests that in general the safest method of prevention is graded ascent, it is not always clear which of the alternative strategies is to be preferred if, for some reason, this is not possible, nor what the major adverse effects of combined approaches might be.

Previously, we assessed six groups of the most common interventions for the prevention of HAI (Nieto 2017). In this Cochrane Review we assess five classes of pharmacological interventions less commonly recommended for this condition. Those classes are as follows.

1. Selective 5-hydroxytryptamine(1) receptor agonist: sumatriptan (Jafarian 2007).
2. N-methyl-D-aspartate (NMDA) antagonist: magnesium (Dumont 2004).
3. Endothelin-1 antagonist: bosentan (Modesti 2006).
4. Anticonvulsant drugs: gabapentin (Jafarian 2008); phenytoin (Wohns 1986).
5. Spironolactone (Currie 1976; Jain 1986; Meyers 1980; Snell 1977; SPACE 2011; Spironolactone in acute mountain sickness 1977; Turnbull 1980).

How the intervention might work

Extensive reviews for the pharmacotherapy of HAI have recently been published (Maggiorini 2010; Wright 2008). Below is a list and brief description of the less common classes of drugs that have been suggested to date. Appendix 3 provides more detail and discusses the potential adverse effects of each class.

1. Selective 5-hydroxytryptamine(1) receptor agonist (sumatriptan): a drug of the family of triptans, characterized by having an agonist effect on vascular serotonin 5-hydroxytryptamine (5-HT1) receptors located in the blood vessels of the brain. The binding of sumatriptan to the 5-HT1

receptor constricts specific large cranial blood vessels without compromising cerebral flow (Jafarian 2007).

2. N-methyl-D-aspartate (NMDA) antagonist: magnesium. NMDA receptors are cell components in glutamate-dependent neuronal synapses, which regulate the entry of calcium and the potential for excitatory neurons. It has been noticed that, in the presence of prolonged stimulus, NMDA receptors favour the accumulation of calcium in neurons and its consequent degeneration. The antagonistic drugs of NMDA, such as magnesium, block these receptors and prevent calcium entering neurons, as well as decrease the changes in their structure and function (Gathwala 2006).

3. Endothelin-1 antagonist (bosentan): endothelin 1 is a peptide produced in the endothelium, which binds to its receptors in the lung capillaries, and stimulates the growth of smooth muscle and blood vessel contraction, which is increased at high altitude too. Bosentan is a competitive antagonist of endothelin-1 receptors, which produces vasodilation and decreased pulmonary vascular resistance (Bevacqua 2013; Goerre 1995; Yanagisawa 1988).

4. Anticonvulsant drugs (gabapentin, phenytoin). Gabapentin is a derivative of the neurotransmitter gamma-aminobutyric acid (GABA) which partially reduces the response to stimulation of the NMDA receptors, preventing development of neuronal excitation and convulsions; it has also been suggested that it may decrease associated pain. Its mechanism of action is currently unknown (Cheng 2006; Maneuf 2006; Mathew 2001). Phenytoin is an anticonvulsant agent which binds to voltage gated sodium channel, inhibits the entry of sodium into the neuron and slows the release of potassium, which prevents neuronal depolarization and favouring cerebral protection (Burse 1982).

5. Spironolactone is a potassium-sparing diuretic that acts by antagonism of aldosterone in the distal renal tubules, increasing the secretion of water and sodium and decreasing the excretion of potassium. (Brookfield 1977; Currie 1976; Jain 1986; Meyers 1980; Snell 1977; Spironolactone in acute mountain sickness 1977; Turnbull 1980).

See Appendix 3 for adverse events of the pharmacological interventions.

Why it is important to do this review

It is important to conduct this systematic review for several reasons.

1. Many people travel to recreational areas located at high altitude, putting themselves at an increased risk of developing acute HAI. HAI may be severe and life-threatening, so effective prevention is likely to be of great value both to these visitors to high altitude areas, and to those responsible for their treatment and rescue when required. At the other end of the spectrum, reliable prevention of minor degrees of AMS would greatly enhance the experience of many travellers. Travel to high altitudes may also aggravate underlying illnesses, particularly cardiopulmonary diseases (CATMAT 2007).

2. The true role of the approaches for preventing acute HAI is uncertain (Adams 2004; Bärtsch 2004; CATMAT 2007; Elphick 2004), meaning that their clinical effectiveness and safety must be assessed.

3. It is necessary to answer questions such as: are all these interventions equally useful regardless of the type of HAI? Is there reason to believe that some forms are more appropriate for some patients (persons at risk) than others?

4. An updated meta-analysis on AMS prevention needs to be produced (Dumont 2000).

Finally, a systematic review including a rigorous assessment of the risk of bias of the most up-to-date evidence will help clinicians make informed decisions regarding the use of non-pharmacological and pharmacological interventions for preventing acute HAI. The protocol of this review included all agents to prevent high altitude illness (Martí-Carvajal 2012), but we decided to split that review into a series of three publications about the prevention of this condition (Part 1: Commonly used drugs. Part 2: Less commonly used drugs. Part 3: Miscellaneous and non-pharmacological interventions). The present review is the second in the series of three and includes five classes of the less frequently recommended drugs to prevent acute HAI conditions.

OBJECTIVES

To assess the clinical effectiveness and adverse events of five of the less commonly used pharmacological interventions for preventing acute HAI in participants who are at risk of developing high altitude illness in any setting.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) irrespective of publication status (unpublished trials or published as articles, abstracts, or letters), language and country. We applied no restrictions with respect to periods of follow-up.

We excluded quasi-randomized studies and prospective observational studies for evaluating clinical effectiveness.

Types of participants

We included trials involving participants who are at risk of developing high altitude illness (such as AMS or HACE, or HAPE, or both). We included participants with and without a history of high altitude illness. We applied no age or gender restrictions.

Types of interventions

The published protocol of this review included all agents to prevent high altitude illness (Martí-Carvajal 2012). However we decided to split the topic into a series of three publications about the prevention of this condition (See Differences between protocol and review section). This is the second of three reviews and includes the following five groups of the less common classes of drugs used to prevent acute HAI.

1. Selective 5-hydroxytryptamine(1) receptor agonist (sumatriptan).
2. N-methyl-D-aspartate (NMDA) antagonist (magnesium).
3. Endothelin-1 antagonist (bosentan).
4. Anticonvulsant drugs (gabapentin; phenytoin).
5. Spironolactone.

We included trials where the relevant medication was administered before the beginning of ascent. We excluded trials using these drugs during ascent or after ascent.

Types of outcome measures

The following outcome measures were modified from the published protocol (Martí-Carvajal 2012). This is a change to the protocol and is explained in the Differences between protocol and review section.

Primary outcomes

1. Risk of acute mountain sickness (AMS - as defined by each study) at any time

Secondary outcomes

1. Risk of high altitude pulmonary oedema (HAPE - as defined by each study) at any time.
2. Risk of high altitude cerebral oedema (HACE - as defined by each study), at any time.
3. Risk of adverse events in general, including paraesthesia, at any time.
4. Differences in HAI/AMS scores at high altitude. We analysed the differences between groups in any measure of AMS severity and between the first to the 48th hour at high altitude.

Search methods for identification of studies

The same search methods were used for the identification of potential studies and are common for the three reviews included in this set.

Electronic searches

We identified RCTs through literature searching with systematic and sensitive search strategies as outlined in Chapter 6.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not apply restrictions to language or publication status.

We searched the following databases for relevant trials.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 4) in the Cochrane Library (searched 20 May 2017);
2. MEDLINE (Ovid SP, 1966 to May week 3 2017);
3. Embase (Ovid SP, 1988 to May week 3 2017);
4. LILACS (BIREME, 1982 to May 2017).

We developed a subject-specific search strategy in MEDLINE and used that as the basis for the search strategies in the other databases listed. Where appropriate, the search strategy was expanded with search terms for identifying RCTs. All search strategies can be found in Appendices 4 to 7 (Appendix 4; Appendix 5; Appendix 6; Appendix 7).

We scanned the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) for ongoing and unpublished trials (May 2017; Appendix 8). The search strategy was developed in consultation with the Cochrane Anaesthesia, Critical and Emergency Care Group Information Specialist.

Searching other resources

We scanned the reference lists and citations of included trials and any relevant systematic reviews that we identified for further references to additional trials.

Data collection and analysis

Data collection and analysis methods were common for the three reviews included in this series.

Selection of studies

Two review authors independently assessed each reference identified by the search against the inclusion criteria. We resolved any disagreements by discussion; a third author was consulted as an arbiter if we could not reach agreement. We retrieved in full those references which appeared to meet the inclusion criteria for further independent assessment by the same three review authors.

Data extraction and management

We used a pre-defined form to extract the following data: eligibility criteria, demographics (age, gender, country), rate of ascent (m/h), final altitude reached (m), AMS scale, design study, history of HAI, type of HAI, proposed intervention, and main outcomes, among others; (see Appendix 9 for details of the data extraction form). For eligible studies, two review authors extracted the data using the selected form. We resolved discrepancies through discussion or, if required, we involved a third author of this review. We entered data into Review Manager 5 (RevMan 5) software and checked it for accuracy.

Assessment of risk of bias in included studies

Three review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion. We judged the methodological quality of each study using Cochrane's tool for assessing risk of bias, a two-part tool that addresses the following six specific domains: random sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective reporting; and other bias (Higgins 2011). The first part describes the risk of bias; the second part provides criteria for making judgements about the risk of bias from each of the six domains in the tool (Appendix 10). Based on this tool we implemented a 'Risk of bias' worksheet to be filled out for each study. The risk of bias was assessed by two authors in an independent fashion. We resolved any disagreement through consultation with an additional author. We displayed the results by creating a 'Risk of bias' graph and a 'Risk of bias' summary figure using RevMan 5 software, if appropriate. We present the risk of bias in the Results section. Likewise, we provide summary assessments of the risk of bias for each outcome within and across studies.

Measures of treatment effect

For dichotomous outcomes (such as risk of AMS or HAPE), we show results as summary risk ratios with 95% confidence intervals (CI). For continuous outcomes (such as differences in AMS scores), we present the results as summary mean differences (MD) or standardized mean differences (SMD) as appropriate, with 95% CI. For individual studies, we used the CS command in STATA 14.0 (www.stata.com/stata14), for estimation of risk ratios with the corresponding 95% CI. This is a change to the protocol (Martí-Carvajal 2012), and is explained in the Differences between protocol and review section. In addition, because we identified a considerable number of cross-over trials concerning assessed interventions, we included these studies separately and analysed this information using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 16.4 (Elbourne 2002; Higgins 2011; Stedman 2011), specially related to estimation of Mantel-Haenszel odds ratio (OR) for paired outcomes.

Unit of analysis issues

Martí-Carvajal 2012 (the published protocol) did not include considerations about any unit of analysis issues. However, we identified 12 cross-over studies in our search strategies and they were included in the analyses, but separate from the parallel studies. In brief, we used the methods recommended by Elbourne (Elbourne 2002; Stedman 2011). This is a change to the protocol (Martí-Carvajal 2012), and is explained in the Differences between protocol and review section.

Dealing with missing data

For all outcomes we carried out analyses on an intention-to-treat (ITT) basis as far as possible (i.e. we attempted to include all randomized participants in the denominator of the assessed groups in the analyses). Due to the fact that we included studies with missing information (especially standard deviations) or data not suitable for planned analyses, we followed the methods recommended by the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 16.1.3 (Higgins 2011). In brief, we transformed median values and their interquartile ranges or range extracted from included studies to means and standard deviations according to Wan and colleagues (Hozo 2005; Wan 2014). This is a change to the protocol (Martí-Carvajal 2012), and is explained in the Differences between protocol and review section.

Assessment of heterogeneity

We used the I^2 statistic to measure statistical heterogeneity among the trials in each analysis. When we identified substantial heterogeneity, we explored it by prespecified subgroup analysis. The I^2 statistic describes the percentage of total variation across trials due to heterogeneity rather than sampling error (Higgins 2003). We considered there to be significant statistical heterogeneity if I^2 was greater than 50% (Higgins 2011). We assessed clinical and methodological diversity of the included studies in a comparison for sufficient homogeneity before choosing to estimate summary effect sizes.

Assessment of reporting biases

We planned to assess whether the review is subject to publication bias by using a funnel plot to graphically illustrate variability between trials. If asymmetry had been detected, we planned to explore causes other than publication bias. We planned to perform a funnel plot if we included 10 or more RCTs for comparison. However, due to scarcity of information we were not able to perform the mentioned analysis. This is a change to the protocol (Martí-Carvajal 2012), and is explained in the Differences between protocol and review section.

Data synthesis

We summarized the findings using the random-effects (DerSimonian-Laird) model. We carried out statistical analyses using RevMan 5 (Review Manager 2014). We accepted important differences where the effect size 95% confidence limits do not cross the value of no difference between groups. We planned to apply trial sequential analysis (TSA), as cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of the accumulating data (Brok 2009; Lan 1983; Thorlund 2009; Wetterslev 2008; Wetterslev 2017). However, due to the scarcity of data for the assessed comparisons in this review, we decided not to report the TSA results in this case (all of them having only one study). This is a change from the published protocol (Martí-Carvajal 2012); (see the details in the Differences between protocol and review section). We will use TSA methods in our update if there are sufficient studies.

Subgroup analysis and investigation of heterogeneity

We investigated heterogeneity by an informed clinical evaluation of each outcome, combining data only when clinically appropriate. We also investigated statistical heterogeneity using the I^2 statistic as described above. For the primary outcomes, we considered subgroup analysis for the following factors, as appropriate.

1. Extreme altitude exposure versus high or very high exposure (high: 1500 to 3500 m; very high: 3500 to 5500 m; and extreme: above 5500 m) (Paralikar 2010).
2. Presence or absence of people at high risk of HAI.
3. Presence or absence of significant pre-existing disease: cardiovascular diseases, chronic obstructive pulmonary disease (COPD), diabetes mellitus.

However, due to scarcity of information we were not able to perform the planned analysis. This is a change to the protocol (Martí-Carvajal 2012), and is explained in the Differences between protocol and review section.

Sensitivity analysis

We performed a sensitivity analysis comparing the general results versus RCTs with high methodological quality (studies classified as having a 'low risk of bias' (Higgins 2011)). We chose only three core domains: generation of allocation sequence, incomplete outcome data, and selective reporting bias. However, due to scarcity of information we were not able to perform the planned analysis. This is a change to the protocol (Martí-Carvajal 2012), and is explained in the Differences between protocol and review section.

'Summary of findings' tables and GRADE

We developed 'Summary of findings' tables for the following comparisons.

1. Sumatriptan compared with placebo (Summary of findings for the main comparison).
2. Magnesium citrate compared with placebo (Summary of findings 2).
3. Spironolactone compared with placebo (Summary of findings 3).
4. Acetazolamide compared with spironolactone (Summary of findings 4).

We highlighted the quality of evidence in four major outcomes: risk of AMS, risk of HAPE, risk of HACE and risk of adverse events.

We used the five GRADE criteria (study limitations; consistency of effect; imprecision; indirectness; and publication bias) to assess the quality of evidence relating to the studies that contributed data to the analyses for each of these four outcomes. When we identified an issue that we considered to be serious in each of the five GRADE criteria, we downgraded the quality of evidence by one level; and when we considered the issue to be very serious, we downgraded the quality of evidence by two levels (Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h). Whenever we decided to downgrade the quality of evidence from the default high quality, we justified our decisions and described the level of downgrade in the footnotes of the table. We developed the 'Summary of findings' table using a web-based version of the GRADEpro software(www.guidelinedevelopment.org), according to the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

RESULTS

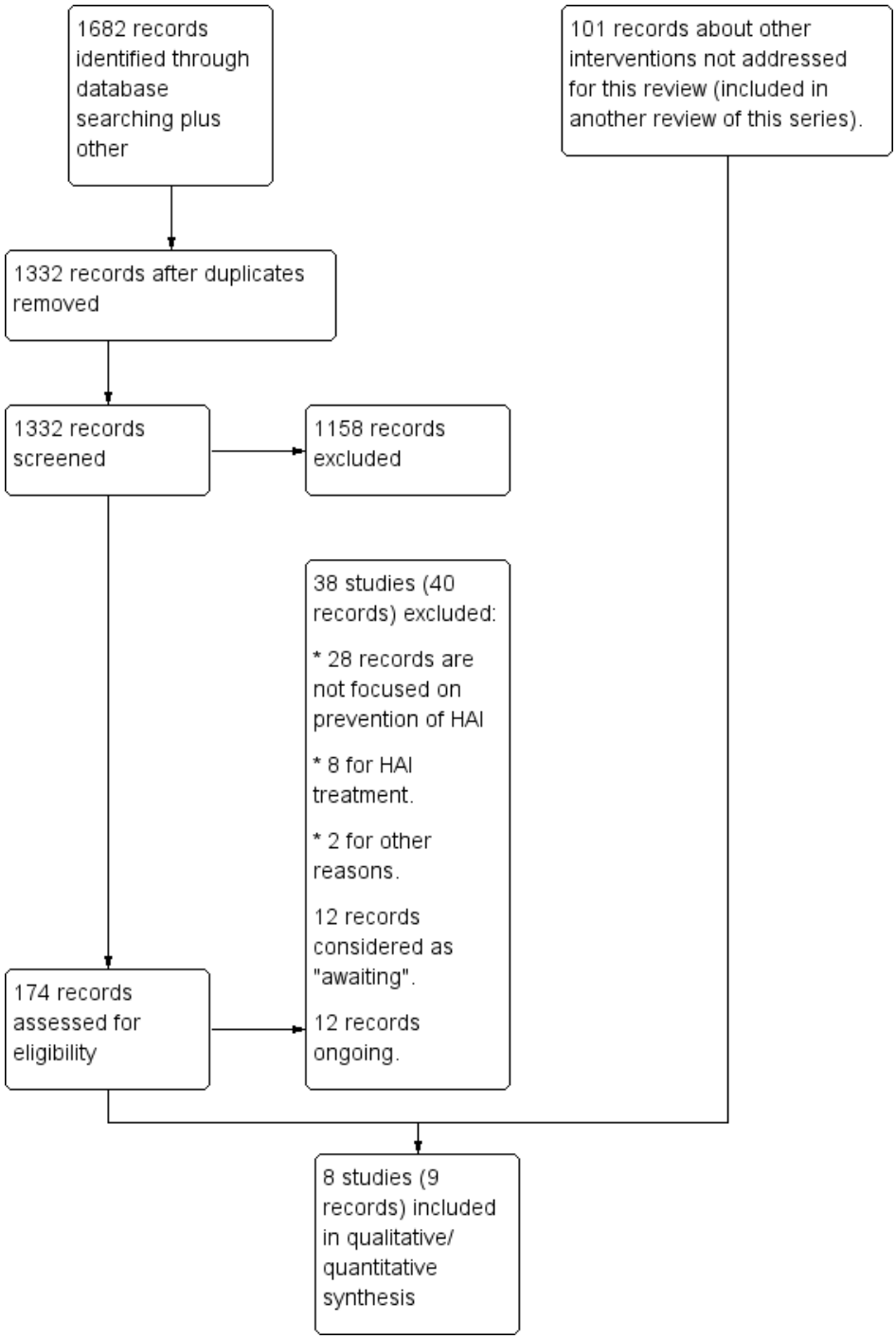
Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

Our searches in May 2017 identified a total of 1332 references. After reviewing the references by title and abstract, we selected 174 of the citations to review as full texts (see Figure 1). After reading the articles we included in this review eight studies (334 participants), distributed in nine references. We excluded 38 studies (distributed in 40 references), and classified a further 12 studies as ongoing, and another 12 studies as awaiting assessment (most of them due to the full text not yet being available). A further 101 studies were not included in the present review: this is because they are due to be included in the other two reviews in this series of three reviews.

Figure 1. Study flow diagram.



Included studies

We included eight studies (334 participants) in this review (Brookfield 1977; Dumont 2004; Jafarian 2007; Jafarian 2008; Jain 1986; Larsen 1986; SPACE 2011; Wohns 1986). The results of Dumont 2004 were published across two separate papers and so is included as a single study. Seven of the eight included studies were parallel trials, while the remaining trial was a cross-over trial (Larsen 1986). All trials were developed at high altitude.

Participants

The participants' ages ranged between 15 and 65 years. Four of the studies included only men (50%; Jafarian 2008; Jain 1986; Larsen 1986; Wohns 1986). Only Dumont 2004 included people with a history of AMS (12.5%).

Setting

Two of the eight included studies were undertaken in the USA (25%; Jain 1986; Larsen 1986). The remaining six studies were carried out in Asia (37.5%; Jafarian 2008; SPACE 2011; Wohns 1986); and in Europe, Africa and South America (37.5%; Brookfield 1977; Dumont 2004; Jafarian 2007).

Administration of intervention to prevent HAI conditions

Three of the eight studies provided the intervention less than 24 hours prior to the ascent (37.5%; Jafarian 2007; Jafarian 2008; Wohns 1986), and four studies between one to three days prior (50%). One trial did not provide information about this issue (SPACE 2011). In 25% of the trials, the participants hiked (trekked) to endpoint altitude, and in the remaining studies they used a combination of means of transportation, including cars, trains, and cable cars (75%).

Altitude

All of the included studies reached a final altitude of between 3500 and 5895 metres above sea level. The difference between the endpoint and the baseline altitude ranged from 700 to 5120 metres. The most frequent durations for ascent were more than two days (four studies; Brookfield 1977; Dumont 2004; SPACE 2011; Wohns 1986). Two studies did not provide any information about these issues (25%; Jain 1986; Larsen 1986).

Scale used to assess AMS

The most commonly used scale used was the Lake Louise Score (50%; Dumont 2004; Jafarian 2007; Jafarian 2008; SPACE 2011), and the criterion to define AMS onset was a score of 3 points or more in two trials (Jafarian 2007; Jafarian 2008). In two studies, the criteria used to define the onset of AMS were unclear (25%; Jain 1986; Larsen 1986).

Funding

Only one of the included studies did not provide clear information about the source of funding (12.5%; Larsen 1986). None of the included studies bar Jafarian 2008 declared their possible conflicts of interests (87.5%). For further information refer to the table 'Characteristics of included studies'

Excluded studies

We excluded 38 studies (40 references) from this series of three reviews (ACME-1 2006; Agostoni 2013; Bartsch 1993; Bartsch 1994; Bilo 2015; Bloch 2009; Broome 1994; Cain 1966; Debevec 2015; Dumont 1999; Forster 1982; Forwand 1968; Fulco 2011; Gertsch 2002; Gray 1971; Harris 2003; Johnson 1988; Jonk 2007; Kotwal 2015; Lalande 2009; Lawley 2012; Levine 1989; Liu 2013; Mairer 2012; McIntosh 1986; Purkayastha 1995; Reinhart 1994; Sandoval 2000; Scalzo 2015; Serra 2001; Siebenmann 2011; Singh 1969; Solís 1984; Suh 2015; Teppema 2007; Vuyk 2006; White 1984; Wright 1988). Twenty-eight (73.6%) out of the 38 studies were excluded because they did not focus on HAI prevention: instead they reported physiological or laboratory results related to altitude ascent. In eight of the excluded studies, the authors reported results for the treatment of HAI conditions (21%). The remaining references were excluded for other reasons.
For further information refer to the table Characteristics of excluded studies.

Studies awaiting classification

We classified 12 studies as awaiting assessment (Dugas 1995; Ellsworth 1987; Furian 2016; Hefti 2014; Kasic 1991; Lee 2011; Pun 2014; Roncin 1996; Swenson 1997; Utz 1970; Wang 1998; Xiangjun 2014). This is because we were unable to obtain the full texts from the authors, the Anaesthesia, Critical and Emergency Care Group (ACE) or the Iberoamerican Cochrane Centre. For further information refer to the table Characteristics of studies awaiting classification.

Ongoing studies

We considered an additional 12 studies as ongoing given that we were only able to find them cited in trial registers, but we considered that they could be due for publication shortly (ChiCTR-TRC-13003319; ChiCTR-TRC-13003590; NCT00886912; NCT01606527; NCT01682551; NCT01794078; NCT01993667; NCT02244437; NCT02450968; NCT02604173; NCT02811016; NCT02941510). For further information refer to the table Characteristics of ongoing studies.

Risk of bias in included studies

The risk of bias for the studies was assessed in seven categories. We provide a summary of our assessment of the methodological quality of included studies in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

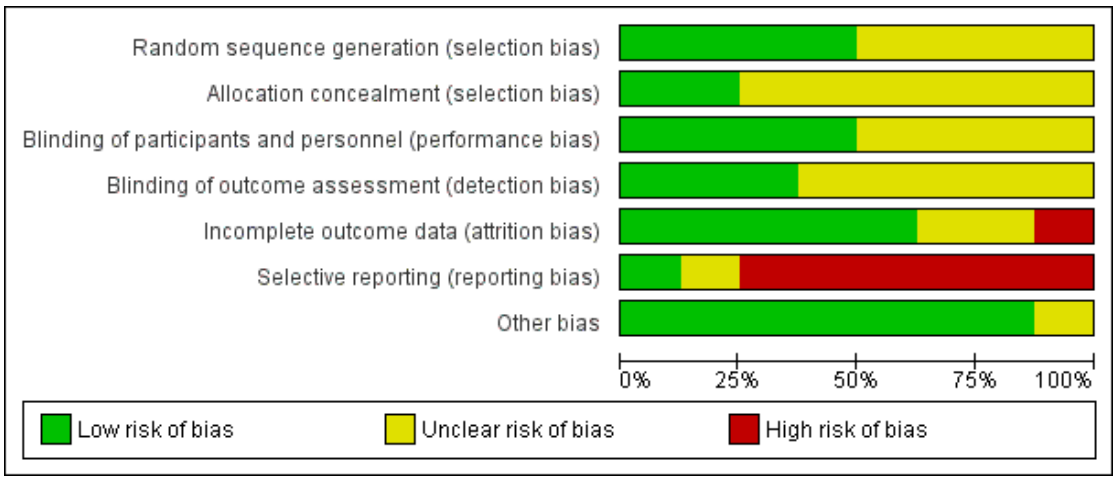
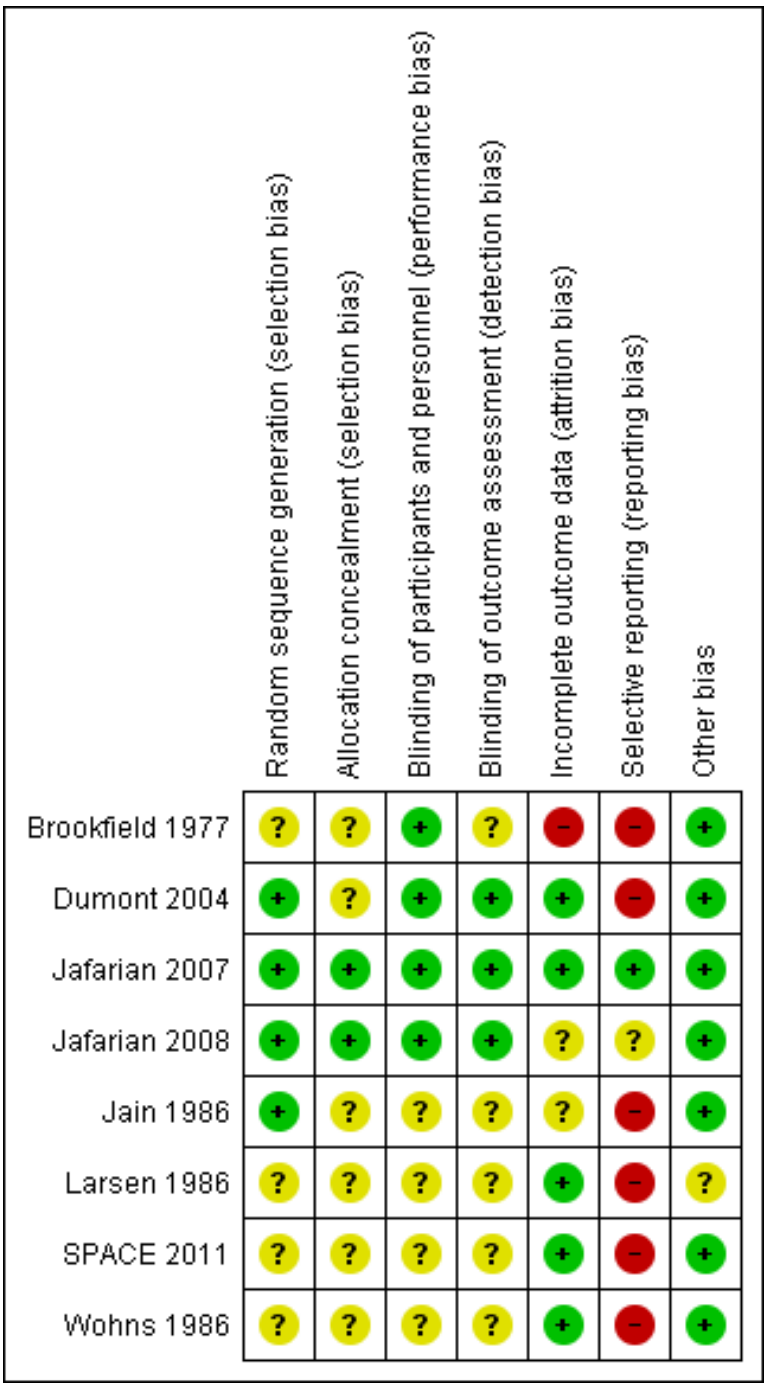


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In four studies, the authors reported a valid method of randomization (Dumont 2004; Jafarian 2007; Jafarian 2008; Jain 1986), whereas this information was not clearly reported in the remaining studies (50%). Similarly, only two studies undertook and reported random allocation concealment (Jafarian 2007; Jafarian 2008), and the information was absent in the remaining included studies (75%).

Blinding

Four studies reported adequate blinding of participants and personnel (Brookfield 1977; Dumont 2004; Jafarian 2007; Jafarian 2008). In the remaining four studies, this domain was classified as unclear (Jain 1986; Larsen 1986; SPACE 2011; Wohns 1986). Regarding detection bias, the risk was considered as low in only three studies (Dumont 2004; Jafarian 2007; Jafarian 2008), whereas this information was considered as unclear in the remaining studies (62%). In three of the studies, the risk of bias was classified as low for both blindings (Dumont 2004; Jafarian 2007; Jafarian 2008).

Incomplete outcome data

Significant numbers of participants were lost or excluded from the final analysis of one study (Brookfield 1977). Two further studies presented unclear data (Jafarian 2008; Jain 1986). In the remaining five studies, the risk of bias was classified as low (62.5%).

Selective reporting

Reporting adverse events associated with the different types of interventions is fundamental for the complete assessment of their usefulness in clinical practice. We found that all studies bar one did not report other adverse events associated with the classes of drugs commonly used for prevention of AMS (such as paraesthesia: Brookfield 1977; Dumont 2004; Jain 1986; Larsen 1986; SPACE 2011; Wohns 1986); and Jafarian 2008 reported unclear information for side effects.

Other potential sources of bias

We found an unclear source of bias in Larsen 1986, because it is unclear whether previous events of HAI (specifically in phase 1) affects the probability of new events in the second phase of cross-over trials. We identified no additional sources of risk in the remaining studies.

Effects of interventions

See: **Summary of findings for the main comparison** Sumatriptan compared with placebo for preventing high altitude illness; **Summary of findings 2** Magnesium citrate compared with placebo for preventing high altitude illness; **Summary of findings 3** Spironolactone compared with placebo for preventing high altitude illness; **Summary of findings 4** Acetazolamide compared with spironolactone for preventing high altitude illness
See Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4

Comparison 1: selective 5-hydroxytryptamine(1) receptor agonist: sumatriptan versus placebo

For this comparison, we analysed the information from one study (Jafarian 2007), with a total of 102 participants. The dosage used was 50 mg/day, and the study was developed in Iran, reaching a maximum altitude of 3500 metres.

Primary outcome 1: risk of acute mountain sickness (AMS)

Jafarian 2007 provided information about the risk of AMS, with a total of 30 events (9/51 (17.6%) in the sumatriptan group versus 21/51 (41.1%) taking the placebo). AMS was defined as a Lake Louise AMS score of 3 or higher, with headache. The estimated RR for AMS, comparing sumatriptan versus placebo, was 0.43 (95% CI 0.21 to 0.84; 102 participants). We downgraded the quality of evidence from high to low due to imprecision issues (See Summary of findings for the main comparison).

Secondary outcome 1: risk of high altitude pulmonary oedema (HAPE)

We found no information about this outcome in the included study.

Secondary outcome 2: risk of high altitude cerebral oedema (HACE)

We found no information about this outcome in the included study.

Secondary outcome 3: risk of adverse events

We found no information about this outcome in the included study.

Secondary outcome 4: differences in HAI/AMS scores

Jafarian 2007 reported a lower Lake Louise AMS score in the sumatriptan group (51 participants; median = 3, IQR = 3) than placebo group (51 participants; median = 1.5, IQR = 2.75; P = 0.005). We were unable to transform this information to means and standard deviations.

Comparison 2: N-methyl-D-aspartate (NMDA) antagonist: magnesium citrate versus placebo

For this comparison we analysed the information from one study (Dumont 2004), with a total of 70 participants. The dose used was 1200 mg/day, and the study was planned in Switzerland, and undertaken in Italy, reaching a maximum altitude of 4559 metres. There were 20 participants with a history of AMS (10 in each group).

Primary outcome 1: risk of acute mountain sickness (AMS)

Dumont 2004 provided information about the risk of acute mountain sickness and found a total of 23 events (12/35 (34.2%) of those taking magnesium versus 11/35 (31.4%) of those taking placebo). AMS was defined as a Lake Louise AMS score greater than 6 with headache score greater than 2 and gastrointestinal/ataxias score greater than 2. The estimated RR for AMS, comparing magnesium citrate tablets versus placebo, was 1.09 (95% CI 0.55 to 2.13; 70 participants). We downgraded the quality of evidence from high to low due to imprecision issues (See Summary of findings 2).

Secondary outcome 1: risk of high altitude pulmonary oedema (HAPE)

We found no information about this outcome in the included study.

Secondary outcome 2: risk of high altitude cerebral oedema (HACE)

We found no information about this outcome in the included study.

Secondary outcome 3: risk of adverse events

Dumont 2004 provided information about the risk of loose stools and they found a total of 17 events (13/35 (37.1%) in those taking magnesium versus 4/35 (11.4%) of those taking placebo). The estimated RR for this adverse event, comparing magnesium citrate versus placebo, was 3.25 (95% CI 1.17 to 8.99; 70 participants). We downgraded the quality of evidence from high to moderate due to imprecision (see Summary of findings 2).

Secondary outcome 4: differences in HAI/AMS scores

We found no information about this outcome in the included study.

Comparison 3: endothelin-1 antagonist - bosentan versus placebo

We did not find trials which evaluate the role of bosentan in prevention of HAI conditions.

Comparison 4: Anticonvulsant drugs - phenytoin versus placebo

For this comparison, we identified one study with a total of 21 participants (Wohns 1986). However this study did not provide information about any of the outcomes selected for this review. This study was planned in the USA and undertaken in Nepal, reaching a maximum altitude of 5120 metres. All the participants in this study were climbers.

Comparison 5: Spironolactone versus placebo

For this comparison, we analysed the information from two studies with a total of 205 participants (Brookfield 1977; SPACE 2011). Investigators administered 75 mg/day in Brookfield 1977 and 100 mg/day in SPACE 2011. The studies were planned in the USA and Nepal and undertaken in Tanzania and Nepal, reaching a maximum altitude of 5898 and 5000 metres respectively. We also included one cross-over study (Larsen 1986), with a total of 12 participants. However, this study did not provide information about any of the outcomes assessed in this review and did not contribute to any analysis.

Primary outcome 1: risk of acute mountain sickness (AMS)

Two studies provided information about the risk of acute mountain sickness (Brookfield 1977; SPACE 2011). A pooled analysis had an I^2 of 72% and this could not be explained by any of our planned subgroup analyses. We have therefore not pooled the results of these trials. Brookfield 1977 defined AMS as a clinical score (not defined) equal to or greater than 2 and reported AMS in 2/6 (33%) of participants taking spironolactone versus 5/6 (83%) of those taking placebo, RR 0.40 (95% CI 0.12 to 1.31). SPACE 2011 defined AMS as a Lake Louise AMS score of headache and one additional symptom and reported AMS in 27/114 (23.6%) in those taking spironolactone versus 13/79 (16.5%) of those taking placebo, RR 1.44 (95% CI 0.79 to 2.01). These studies differ in terms of final altitude reached (5895 m versus 5000 m, respectively). We downgraded the quality of evidence from high to very low due to study limitations suggesting there may be a high risk of bias, inconsistency and imprecision with these two studies; (see Summary of findings 3). We were unable to perform TSA due to high heterogeneity for this comparison.

Secondary outcome 1: risk of high altitude pulmonary oedema (HAPE)

SPACE 2011 researchers assessed the risk of altitude pulmonary oedema, but they did not find events to report (Table 1). We downgraded the quality of evidence from high to low due to unclear risk of selection, performance and detection bias, as well as imprecision issues (See Summary of findings 3).

Secondary outcome 2: risk of high altitude cerebral oedema (HACE)

SPACE 2011 researchers assessed the risk of altitude cerebral oedema, but they did not find events to report (Table 1). We downgraded the quality of evidence from high to low due to unclear risk of selection, performance and detection bias, as well as imprecision issues (See Summary of findings 3).

Secondary outcome 3: risk of adverse events

We found no information about this outcome in the included study.

Secondary outcome 4: differences in HAI/AMS scores

We found no information about this outcome in the included study

Comparison 6: other comparisons - acetazolamide versus spironolactone

Two studies reported this comparison, enrolling a total of 251 participants. They were conducted in India and Nepal, reaching a final altitude of 3000 and 5000 metres respectively (Jain 1986; SPACE 2011). No primary or secondary outcomes were reported by Jain 1986, so only SPACE 2011 could contribute data to this review. This trial administered 500 mg of acetazolamide/day and 100 mg of spironolactone/day.

Primary outcome 1: risk of acute mountain sickness (AMS)

SPACE 2011 researchers found 37 events of acute mountain sickness for this comparison (10/118 (8.4%) of those taking acetazolamide versus 27/114 (23.6%) taking spironolactone. The estimated RR for AMS, comparing acetazolamide versus spironolactone, was 0.36 (95% CI 0.18 to 0.70); 232 participants). We downgraded the quality of evidence from high to low due to unclear risk of selection, performance and detection bias, as well as imprecision (See Summary of findings 4).

Secondary outcome 1: risk of high altitude pulmonary oedema (HAPE)

The authors of SPACE 2011 did not find any events of high altitude pulmonary oedema. We downgraded the quality of evidence from high to low due to unclear risk of selection, performance and detection bias, as well as imprecision (See Summary of findings 4).

Secondary outcome 2: risk of high altitude cerebral oedema (HACE)

The authors of SPACE 2011 did not find any events of high altitude cerebral oedema . We downgraded the quality of evidence from high to low due to unclear risk of selection, performance and detection bias, as well as imprecision (See Summary of findings 4).

Secondary outcome 3: risk of adverse events

We found no information about this outcome in the one included study.

Secondary outcome 4: differences in HAI/AMS scores

We found no information about this outcome in the one included study.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Magnesium citrate compared with placebo for preventing high altitude illness

Patient or population: participants at risk of high altitude illness
Setting: High altitude (Italy)
Intervention: magnesium citrate
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk placebo	Corresponding risk Magnesium				
Risk of acute mountain sickness	**314 per 1000**	**343 per 1000** (176 to 669)	**RR 1.09** (0.55 to 2.13)	70 (1 study)	⊕⊕◯◯ **Low**[1]	
Risk of high altitude pulmonary oedema- not reported	Not estimable	Not estimable	Not estimable			Not reported
Risk of high altitude cerebral oedema- not reported	Not estimable	Not estimable	Not estimable			Not reported
Risk of adverse events: Loose stools	**114 per 1000**	**371 per 1000** (134 to 1000)	**RR 3.25** (1.17 to 8.99)	70 (1 study)	⊕⊕◯◯ **Low**[1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: we are very uncertain about the estimate.

[1] Imprecision downgraded by 2 levels due to insufficient sample size to determine whether there are differences or no differences between these 2 groups.

Spironolactone compared with placebo for preventing high altitude illness

Patient or population: participants at risk of high altitude illness
Setting: High altitude (Tanzania)
Intervention: spironolactone
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Spironolactone				
Risk of acute mountain sickness	Not estimable	Not estimable		205 (2 studies)	⊕○○○ **Very low**[1]	RR ranged from 0.40 to 1.44
Risk of high altitude pulmonary oedema	Not estimable	Not estimable	Not estimable	193 (1 study)	⊕⊕○○ **low**[2]	No HAPE events recorded
Risk of High altitude**cerebral oedema**	Not estimable	Not estimable	Not estimable	193 (1 study)	⊕⊕○○ **low**[2]	No HACE events recorded
Risk of adverse events - not reported	Not estimable	Not estimable	Not estimable			Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: we are very uncertain about the estimate.

[1] Quality of evidence downgraded from high to very low due to a high risk of bias, imprecision and inconsistency.

2 Quality of evidence downgraded from high to low due to unclear risk of selection, performance and detection bias, as well as imprecision issues

Acetazolamide compared with spironolactone for preventing high altitude illness

Patient or population: participants at risk of high altitude illness
Setting: High altitude (Nepal)
Intervention: spironolactone
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Spironolactone	Acetazolamide				
Risk of acute mountain sickness	**237 per 1000**	**85 per 1000** (43 to 168)	**RR 0.36** (0.18 to 0.70)	232 (1 study)	⊕⊕◯◯ **low**[1,2]	
Risk of high altitude pulmonary oedema	Not estimable	Not estimable	Not estimable	232 (1 study)	⊕⊕◯◯ **low**[1,2]	No HAPE events recorded
Risk of high altitude cerebral oedema	Not estimable	Not estimable	Not estimable	232 (1 study)	⊕⊕◯◯ **low**[1,2]	No HACE events recorded
Risk of adverse events - not reported	Not estimable	Not estimable	Not estimable			not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: we are very uncertain about the estimate.

[1] Risk of bias downgraded by 1 level due to unclear selection, performance and detection bias.

[2] Imprecision downgraded by 1 level due to insufficient sample size to determine whether there are differences or no between these 2 groups.

DISCUSSION

Summary of main results

Evidence from eight studies and 334 participants showed the scarcity of evidence regarding the following five less commonly used classes of drugs for prevention of HAI conditions: selective 5-hydroxytryptamine(1) receptor agonists; N-methyl-D-aspartate (NMDA) antagonist; endothelin-1 antagonist; anticonvulsant drugs; and spironolactone. For most of the assessed comparisons, we only found evidence from a single study. Four studies were at a low risk of bias for randomization, two for allocation concealment. Four studies were at a low risk of bias for blinding of participants and personnel. Three studies were considered at a low risk of bias for blinding of outcome assessors. Most studies were considered at high risk of selective reporting bias.
We report results for the four main comparisons as follows.

Sumatriptan versus placebo (1 parallel study; 102 participants)

Data on sumatriptan showed a reduction of the risk of AMS when compared with a placebo (risk ratio (RR) 0.43 (95% CI 0.21 to 0.84); 1 study; 102 participants; low quality of evidence). This study did not report events of HAPE, HACE or adverse events related to administrations of sumatriptan.

Magnesium citrate versus placebo (1 parallel study; 70 participants)

The estimated RR for AMS, comparing magnesium citrate tablets versus placebo, was 1.09 (95% CI 0.55 to 2.13; 1 study; 70 participants; low quality of evidence). In addition, the estimated RR for loose stools was 3.25 (95% CI 1.17 to 8.99; 1 study; 70 participants; low quality of evidence). The included study did not report events of HAPE or HACE.

Spironolactone versus placebo (2 parallel studies; 205 participants)

Pooled estimation of RR for AMS was not performed due to considerable heterogeneity between included studies (I^2 = 72%). RR from individual studies was 0.40 (95% CI 0.12 to 1.31) and 1.44 (95% CI 0.79 to 2.01; very low quality of evidence). No events of HAPE or HACE were reported. Adverse events were not evaluated.

Acetazolamide versus spironolactone (1 parallel study; 232 participants)

Data on acetazolamide compared with spironolactone showed a reduction of the risk of AMS with the administration of acetazolamide (RR 0.36; 95% CI = 0.18 to 0.70; 232 participants; low quality of evidence). No events of HAPE or HACE were reported. Adverse events were not evaluated.
In addition, we did not find any studies comparing endothelin-1 antagonists (such as bosentan) with a placebo. We also did not find evidence of benefits and harms of anticonvulsant drugs (such as phenytoin), in terms of primary and secondary outcomes selected for our review.

Overall completeness and applicability of evidence

We identified a limited number of studies addressing the effectiveness and safety of the less common pharmacological interventions for the prevention of HAI, with almost all the evidence being specifically about AMS. We included eight studies in this review (334 participants). Few of the included studies reported on our primary and secondary outcomes. The findings of this review should be interpreted carefully in the light of the methodological limitations of the included clinical trials, the lack of information on aspects related to these interventions, as well as the different criteria and scales used (see also Nieto 2017 for more information regarding scales used). It also highlights the lack of reports of adverse events.

Quality of the evidence

We used the GRADE system to assess the quality of the body of evidence associated with primary and secondary outcomes. (See Summary of findings for the main comparison, Summary of findings 2, Summary of findings 3 and Summary of findings 4 for complete assessments and the rationale for ratings.) Risk of bias and imprecision were the GRADE considerations most affected in the assessment of the quality of the evidence in our review, especially for risk of AMS in all comparisons (downgraded two levels in most of the cases). Inconsistency was only detected for the risk of AMS in spironolactone versus placebo (downgraded three levels). Indirectness and publication bias were not detected for the gathered evidence.

Potential biases in the review process

In all cases, we followed the methodology for systematic reviews outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, we had to make extensive modifications to the published protocol (Martí-Carvajal 2012), due to the need to update the methods to the current Methodological Expectations of Cochrane Intervention Reviews (MECIR) (Higgins 2016). For instance, the MECIR guidelines were published after publication of this review's protocol (Martí-Carvajal 2012), and some sections required major post-hoc modifications. At that point we had some knowledge about the results of our search,

and this could have introduced bias in these modifications. All modifications were approved by the Cochrane Anaesthesia, Critical and Emergency Care Group (ACE) editors in collaboration with clinical and statistical experts, and we believe the risk of bias was reduced as far as possible. In addition, one major change was the decision to split the review into three parts, considering the numerous interventions assessed for HAI prevention. This decision was guided by the search results submitted in a first draft of the review, and because the ACE editors considered that the readability of the information could be adversely affected without this division. We believe the subgroups help understanding of the heterogeneity and variability of interventions in this field, as well as allow the presentation of critical information in a clearer manner. We also suggest all these interventions should be analysed in a network meta-analysis, in order to determine which interventions are more effective in avoiding the onset of new cases of this condition. Please see Differences between protocol and review for the full list of the modifications undertaken for this series of reviews about the prevention of HAI.

Twelve potentially eligible studies did not provide enough information to enable us to classify them as included or excluded. This was because they were published only as conference proceedings, or because we did not have access to the full texts when we were completing this review. We also considered 12 additional studies as ongoing because they were published only as protocols.

An additional potential bias in our review was the difficulty we had in contacting trial authors to request additional information. We were unable to undertake this task due to, in most cases, no clear contact information being supplied in the publication. In addition, at least half of the included studies were published more than two decades ago. Trial authors might have been a potential source of information to document the rate of adverse events related to assessed interventions. We found that most of the studies (more than 87%) did not report adverse events associated with the classes of drugs commonly used for the prevention of AMS. This constitutes a lack of information about the safety profile of the drugs in question.

In addition, we did not expect to encounter any unit of analysis issues as we did not expect to find cross-over studies. However, we identified in this review one cross-over study (12 cross-over in total for this series of reviews) in our search strategies. In order to avoid bias in the development of our review, we analysed those studies separately.

Agreements and disagreements with other studies or reviews

Most of the published reviews recommend slow ascent, and acetazolamide or dexamethasone as alternatives for the prevention of this condition (Flaherty 2016; Kayser 2012; Khodaee 2016; Low 2012; Ritchie 2012; Seupaul 2012; Zafren 2014).

CATMAT 2007 proposed a role for spironolactone (25 mg orally four times a day) in prevention of HAI, but accepted this recommendation needed confirmation with further evidence. Likewise, Marmura and colleagues showed that gabapentin and sumatriptan could have a clearer role in treatment of HAI instead of prevention (Marmura 2015). We did not find any reviews about other options such as bosentan, phenytoin or magnesium, and these pharmacological interventions are not recommended in current clinical practice guidelines for the prevention of this condition.

Recently, Davis and colleagues discussed current advances in the prevention and treatment of HAI (Davis 2017). The authors stated that prophylaxis of HAI has as a main goal optimal acclimatization to prevent these conditions, so pharmacological interventions such as acetazolamide remain as the major strategy in AMS and HAPE prevention. In addition, nifedipine and phosphodiesterase inhibitors are also proposed as useful agents in prevention of HAPE. However, none of the drugs included in this review is proposed as having a role in the prevention of HAI conditions (Davis 2017). Likewise, Luks and colleagues stated that pharmacological interventions can be considered for individuals at high risk of developing HAI conditions (Luks 2017). Acetazolamide and dexamethasone have been considered valid alternatives in prevention of AMS; and nifedipine, tadalafil and salmeterol are options considered for HAPE prevention in individuals with a history of this condition (Luks 2017).

AUTHORS' CONCLUSIONS

Implications for practice

The assessment of five of the less commonly used classes of drugs suggests there is little evidence available concerning these interventions in prevention of HAI conditions. Clinical benefits and harms related to these potential interventions remain unclear. Overall, the evidence is of limited practical significance in the clinical field.

Implications for research

There is a lack of large and multi-centre studies of most of the pharmacological agents evaluated in this review. For most of the comparisons evaluated, small sample sizes and lack of reporting of adverse events affect the quality of results. Further studies should also evaluate combinations of pharmacological strategies to prevent HAI. Design of future trials might be improved by the following suggestions.

1. Refining the operative definition of HAI conditions by selecting a unified scale and threshold.

2. Improving the reporting of statistical data related to important outcomes in order to avoid missing data, and inclusion of information about elevation where HAI occurs.

3. Adding adverse events as an important endpoint in assessment of these preventive strategies.

4. Comparing potential pharmacological agents against interventions of well-known effectiveness (such as acetazolamide, an intervention assessed in the first part of this series of reviews).

Finally, we suggest performing a network meta-analysis of all interventions (pharmacological and non-pharmacological) used for high altitude illness prevention, in order to determine which interventions are more effective in avoiding the onset of new cases of this condition.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Brookfield 1977

Methods	Design: parallel - 2 arms Country: Tanzania Multisite: no International: no Treatment duration: 6 days Follow-up: unclear Rate of ascent (m/h): unclear Final altitude reached: 5895 m AMS scale: unclear (arbitrary symptom score) Random unit: participants Analysis unit: groups
Participants	1. 15 participants enrolled (all unacclimatized Europeans living at sea level apart from 1 member normally residing at 2000 m) Participants randomized to: • spironolactone group (unclear number) • placebo group (unclear number) 2. 3 participants were excluded. They dropped out at an altitude of less than 3700 m without evidence of AMS (unclear which group) 12 participants included in analysis • Spironolactone group (n = 6; 50%). • Placebo (n = 6; 50%) 3. Main characteristics of participants: • Age (range): 12 to 35 years • Number of women/men: 10 men and 2 women
Interventions	1. Spironolactone group (intervention): 25 mg tablet, 1 tablet 3 times a day for 6 days 2. Placebo group (control): no details were provided 3. Co-interventions: not stated
Outcomes	1. AMS presence: total score of 2 or more in an arbitrary scale of symptoms, including: 1 point for headache, nausea and insomnia; 2 points each for a headache not relieved by 0.6 mg of aspirin, or vomiting; 3 points each for shortness of breath at rest, severe and inappropriate lassitude, and ataxia 2. Assessment of optic fundi 3. Urine output Outcomes were not classified as primary or secondary.
Notes	1. Trial Registration: not stated. 2. Funder: Pharmacy division, University of Dar es Salaam 3. Role of funder: preparation of tablets 4. A priori sample size estimation: no 5. Conducted: not stated

	6. Declared conflicts of interest: no 7. No contact information supplied in publication; unable to contact authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to score this item as low or high risk of bias Quote: "These were given to all members in a random double-blind basis, neither subjects nor investigators knowing what tablets each person was receiving" (page 689)
Allocation concealment (selection bias)	Unclear risk	Insufficient information to score this item as low or high risk of bias Quote: "These were given to all members in a random double-blind basis, neither subjects nor investigators knowing what tablets each person was receiving" (page 689)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "These were given to all members in a random double-blind basis, neither subjects nor investigators knowing what tablets each person was receiving" (page 689)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to score this item as low or high risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	20% of participants (3) were lost at follow-up
Selective reporting (reporting bias)	High risk	Outcomes important to participants, such as adverse events, were not reported Full information about number of participants at the beginning of the study is not provided (per-protocol analysis)
Other bias	Low risk	No additional biases were identified

Dumont 2004

Methods	Design: parallel design (2 arms), 2 stages: prevention trial and treatment trial Country: Italian Alps (Capanna Regina Margherita) Multisite: no International: no Treatment duration: 5 days Follow-up: 7 days Rate of ascent (m/h): 140 m/h Final altitude reached: 4559 m AMS scale: Lake Louise Consensus Symptom Score
Participants	1. 61 healthy subjects started the prevention trial Exclusion criteria were residency above 600 m; a stay above 2000 m, medication including vitamins or magnesium during the last 3 months; cardiac, pulmonary, neurological, renal hepatic or psychiatric disease 2. Participants randomized to: • magnesium citrate 30 (49.2%) • placebo 31 (50.8%) 3. Participants lost at follow-up: 1 subject (placebo) fell ill before starting the trial and did not turn up; he was not considered for any analysis. 5 subjects (2 in the placebo group and 3 in the magnesium group) had to return from the Capanna Mantova (3420 m) in the morning of day 2 due to bad weather conditions. 1 subject in the magnesium group abandoned due to physical exhaustion on day 2 before reaching the Capanna Regina Margherita. She was evacuated by helicopter and accompanied by 2 colleagues (1 placebo and 1 in the magnesium group). None of these 8 subjects had experienced symptoms of AMS and they were considered for the adverse-effect analysis only 4. Main characteristics of participants (in general): • 29 females, 32 males • age mean: 35.3 ± 8.5 yr • history of AMS: 20/61 (10 in each group)
Interventions	400 mg magnesium/8 hourly/5 days orally Placebo/8 hourly/5 days
Outcomes	Primary outcome • Number of prevention successes Secondary outcomes • Number of prevention failures • Delay until prevention failure • Maximum Lake Louise Scores at any time during the study period
Notes	1. Trial Registration: not stated 2. Funder: Geneva University Hospitals 3. Role of funder: financial support 4. A priori sample size estimation: yes, stated on page 271 5. Conducted: not stated 6. Declared conflicts of interest: not stated 7. No contact information supplied in publication; unable to contact authors
Risk of bias	

Dumont 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A table of random numbers was used for randomization purposes (page 270)
Allocation concealment (selection bias)	Unclear risk	Insufficient information to score this item as low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding was maintained by giving medication in the same fashion. Quote: "Tablets of identical size, colour and taste were taken every 8 hours (...) subjects and investigators were blinded to the assigned treatment" (page 270)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "subjects and investigators were blinded to the assigned treatment" (page 270)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Percentage of participants lost at follow-up: 12.85%
Selective reporting (reporting bias)	High risk	Outcomes important to participants, such as adverse events, were not reported
Other bias	Low risk	No other biases were identified

Jafarian 2007

Methods	Design: parallel (2 arms) Country: Iran Multisite: no International: no Treatment duration: single dose Follow-up: 48 hours Rate of ascent (m/h): 1600 to 3500 within 45 to 60 minutes Final altitude reached: 3500 metres AMS scale: AMS Lake Louise score Random unit: participants Analysis unit: participants
Participants	1. 102 volunteers enrolled (18 to 60 years of age, unacclimatized, and stayed at an altitude of 1200 m to 1500 m for at least 2 weeks before ascent) and randomized 75 ineligible individuals due to: • < 18 or > 60 years (34) • serious hypertension or cardiovascular disease (2) • refused to participate (39) 2. Participants were randomized to:

	• sumatriptan = 51 (50 %) • placebo = 51 (50 %) 3. 5 participants excluded (after randomization) due to private reasons (3 in intervention group and 2 in placebo group) 4. Main characteristics of participants: • Age - mean (IQR): intervention group = 25 (13.2) years; placebo group = 24 (7.5) years • Female sex (%): intervention group = 27.5; placebo group = 29.4 • Percentage of cigarette smokers: intervention group = 54.6; placebo group = 52.9 • Percentage of participants with chronic headache: intervention group = 7.8; placebo group = 5.9
Interventions	1. Sumatriptan group (intervention): 50 mg sumatriptan succinate capsule single dose 2. Placebo group (control): 50 mg identical monohydrate lactose capsule single dose
Outcomes	Primary outcome 1. Number of participants remaining free of AMS during 24 hours Secondary outcomes 1. Severity of AMS and headache 2. Adverse events
Notes	1. Trial Registration: Controlled clinical trial ISRCTN 87201238 2. Funder: Imam Neurology Research Center 3. Role of funder: not stated 4. A priori sample size estimation: yes 5. Conducted: 1 October to 17 November 2006 6. Declared conflicts of interest: not provided 7. No contact information supplied in publication.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned using block randomisation (blocks of 2) to receive either 50mg sumatriptan succinate capsule or identical monohydrate lactose capsule as placebo (Darou Darman Pars Pharmaceuticals, Tehran, Iran) in a non stratified randomisation method." (page 274)
Allocation concealment (selection bias)	Low risk	Quote: "the medications were in opaque boxes labelled with randomisation codes that were not disclosed to clinicians and assessor." (page 274)

Jafarian 2007 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Only the pharmacist who provided the drugs knew the details of computer-generated randomisation codes, and all patients, clinicians, and assessor were unaware of medication type" (page 274)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Only the pharmacist who provided the drugs knew the details of computer-generated randomisation codes, and all patients, clinicians, and assessor were unaware of medication type" (page 274)
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 participants (5/102 = 4.9%) were lost at follow-up
Selective reporting (reporting bias)	Low risk	No selective reporting identified
Other bias	Low risk	No other biases were identified

Jafarian 2008

Methods	Design: parallel (2 arms) Country: Iran Multisite: no International: no Treatment duration: single dose Follow-up: 24 hours Rate of ascent (m/h): 1600 to 3500 within 45 to 60 minutes Final altitude reached: 3500 metres AMS scale: AMS Lake Louise score Random unit: participants Analysis unit: participants
Participants	1. 204 volunteers enrolled (15 to 65 years of age, unacclimatized, and stayed at an altitude of 1200 m to 1500 m for at least 2 weeks before ascent) and randomized Exclusion criteria: history of cardiac or cerebral or pulmonary disease, severely impaired kidney or liver function, use of analgesics or anticonvulsants or tricyclic antidepressants within the previous 48 hours, current history of alcohol or drug abuse, known allergy to gabapentin, pregnancy, and presence of any of the AMS symptoms before the trial 2. Participants were randomized to: • gabapentin = 102 (50%) • placebo = 102 (50 %) 3. No participants were lost at follow-up 4. Main characteristics of participants • Age - mean (SD): intervention group = 31.6 y (12); placebo group = 31.3 y (11.4) • Female sex (%): intervention group = 38.2; placebo group = 36.3 • Percentage of cigarette smokers: intervention group = 24.5; placebo group = 19.6

	• Percentage of migraine history: intervention group = 10.8; placebo group = 11.8
Interventions	1. Gabapentin group (intervention): 600 mg gabapentin lactose capsule single dose 2. Placebo group (control): 600 mg identical monohydrate lactose capsule single dose
Outcomes	Primary outcome 1. HAH risk and intensity 2. Duration of moderate/severe headache-free phases after the beginning of the trial Secondary outcomes 1. Risk and severity of AMS 2. Adverse events
Notes	1. Trial Registration: ISRCTN26123577 2. Funder: Imam Neurology Research Center. Darou Darman Pars Pharmaceuticals 3. Role of funder:Provision of gabapentin and placebo 4. A priori sample size estimation: no 5. Conducted: February to April 2007 6. Declared conflicts of interest: yes 7. No contact information supplied in publication.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Subjects who were found to be eligible at screening were randomised in a 1:1 ratio (in blocks of six) to one of two treatment groups using a computer generated randomisation schedule" (page 321)
Allocation concealment (selection bias)	Low risk	Quote: "Medications were presented in identical opaque boxes that were labelled with their randomisation numbers; these numbers were not disclosed to clinicians and the assessor. Only the pharmacist who provided the drugs knew the details of the codes" (page 321)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Medications were presented in identical opaque boxes that were labelled with their randomisation numbers; these numbers were not disclosed to clinicians and the assessor. Only the pharmacist who provided the drugs knew the details of the codes" (page 321)

Jafarian 2008 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Medications were presented in identical opaque boxes that were labelled with their randomisation numbers; these numbers were not disclosed to clinicians and the assessor. Only the pharmacist who provided the drugs knew the details of the codes" (page 321)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No participants were lost at follow-up
Selective reporting (reporting bias)	Unclear risk	Adverse events are not reported in a full way
Other bias	Low risk	No other biases were identified

Jain 1986

Methods	Design: randomized blind trials Country: Delhi, India Multisite: no International: no Treatment duration: Four days Follow-up: 4 days Rate of ascent (m/h): simulate 4570 m in 1 day Final altitude reached: 4570 m AMS scale: General High Altitude Questionnaire (GHAQ) Random unit: random number table and in a blind fashion Analysis unit: unclear
Participants	1. 29 participants enrolled (healthy Indian soldiers aged between 22 and 26 years having no previous experience of stay at high altitude) Participants randomized to: • acetazolamide (10) • spironolactone (9) • placebo (10) 2. No randomized participants were excluded 3. No participants were lost at follow-up 4. Main characteristics of participants: not reported
Interventions	Acetazolamide tablets 250 mg every 6 hours beginning a day before the actual ascent to high altitude Spironolactone tablets 25 mg every 6 hours beginning a day before the actual ascent to high altitude Placebo tablet every 6 hours beginning a day before the actual ascent to high altitude
Outcomes	• Symptoms of AMS • Blood gas measurement Outcomes were not classified as primary or secondary

Jain 1986 (*Continued*)

Notes	1. Trial Registration: not stated 2. Funder: not stated 3. Role of funder: not stated 4. A priori sample size estimation: no 5. Conducted: 1984 6. Declared conflicts of interest: not reported 7. No contact information supplied in publication; unable to contact authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The subjects were initially tested at an altitude of 200 m and then divided into three groups by using a random number table" (page 294)
Allocation concealment (selection bias)	Unclear risk	Insufficient information to score this item as low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to score this item as low or high risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to score this item as low or high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No participants were reported as lost at follow-up
Selective reporting (reporting bias)	High risk	Outcomes important to participants, such as adverse events, were not reported
Other bias	Low risk	No other biases were identified

Larsen 1986

Methods	Design: cross-over design (2 arms) Country: USA Multisite: no International: no Treatment duration: 4 days Follow-up: 3 weeks Final altitude reached: 4570 m simulated in a hypobaric chamber AMS scale: Environmental Syndrome questionnaire Random unit: participants Analysis unit: participants
Participants	1. 12 male participants enrolled (ages 19 to 25 years, lowland residents who had not been exposed to high altitude for at least 6 months) Exclusion criteria: unclear 2. 3 participants were excluded after randomization: 1 participant excluded for chest pain, 1 for personal reasons, 1 for viral syndrome; 9 completed the cross-over phase 3. No participants were lost at follow-up 4. Main characteristics of participants: not reported
Interventions	• Spironolactone 25 mg 48 hours prior to and 46 hours during exposure • Placebo
Outcomes	• Presence of AMS • Psychological assessment • Biochemical and physiological measurements Outcomes were not classified as primary or secondary
Notes	1. Trial Registration: not stated 2. Funder: not stated 3. Role of funder: not stated 4. A priori sample size estimation: no 5. Conducted: not stated 6. Declared conflicts of interest: not reported 7. No contact information supplied in publication; unable to contact authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to score this item as low or high risk of bias Quote: "Treatment order was randomised between subjects and balanced between trials" (page 544)
Allocation concealment (selection bias)	Unclear risk	Insufficient information to score this item as low or high risk of bias

Larsen 1986 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to score this item as low or high risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to score this item as low or high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were reported as lost at follow-up
Selective reporting (reporting bias)	High risk	Outcomes important to participants, such as adverse events, were not reported
Other bias	Unclear risk	It is unclear if previous events of HAI (specifically in phase 1) affects the probability of new events in second phase of crossover trials

SPACE 2011

Methods	Design: parallel (3 arms) Country: Nepal Multisite: no International: no Treatment duration: 30 h to 4 days Follow-up: unclear Rate of ascent (m/h): unclear Final altitude reached: 5000 m AMS scale: Lake Louise score Random unit: participants Analysis unit: groups
Participants	1. 311 participants enrolled (healthy male and female subjects between 18 and 65 years without AMS or any concurrent illness and not taking acetazolamide) Exclusion criteria: • Mild AMS (more than 1 mild symptom on the LLQ) • Significantly depressed oxygen saturation (< 75%) • Pregnancy or those who could not exclude the possibility of being pregnant or have missed menses by over 7 days • History of allergy to acetazolamide or other sulfa drugs • Individuals who were on ACE inhibitors (e.g. enalapril) or other diuretics (e.g. amiloride or triamterene) • Individuals who had spent 24 hours at an altitude of 4500 m (14,000 ft) within the last 9 days • Individuals known to have taken any of the following in the prior 2 days: acetazolamide (Diamox), steroids • (dexamethasone, prednisone), theophylline, or diuretics (furosemide)

	• Individuals failing to provide informed consent at the study enrolment site at Pheriche Participants randomized to: • 114 spironolactone (36.6%) • 118 acetazolamide (37.9%) • 79 placebo (25.4%) 2. 25 participants randomized (8%, uniformly distributed) were excluded from analysis because they broke the protocol: • Acetazolamide group (8, 7.7 %) • Spironolactone group (10, 9.8%) • Placebo group (7, 9.8%). 3. Participants lost at follow-up: • Acetazolamide group (n = 15, 12%) • Spironolactone group (n = 12, 10.5%) • Placebo group (n = 8, 10%) 4. Main characteristics of participants: • Age (mean, SD): ○ Acetazolamide group: 37 ± 12,2 ○ Spironolactone group: 37.7 ± 12 ○ Placebo group: 39.4 ± 12.1 • Number of men, %: ○ Acetazolamide group: 59 (62.1%) men ○ Spironolactone group: 67 (62.8%) men ○ Placebo group: 46 (71.9%) men
Interventions	1. acetazolamide group: acetazolamide 250 mg twice daily orally for 4 days 2. spironolactone group: Spironolactone 50 mg twice daily orally for 4 days 3. placebo group: placebo twice daily orally for 4 days
Outcomes	Primary outcome • Risk and severity of AMS Secondary outcomes • Risk of headache together with severity AMS • SpO 2
Notes	1. Trial Registration: (ISRCTN77054547) 2. Funder: Wellcome Trust, UK. 3. Role of funder: financial support 4. A priori sample size estimation: no 5. Conducted: 6 October and 24 November 2007 6. Declared conflicts of interest: no 7. No contact information supplied in publication; unable to contact authors.

Risk of bias

Bias	Authors' judgement	Support for judgement

SPACE 2011 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Insufficient information to score this item as low or high risk of bias Quote: "randomisation of spironolactone, acetazolamide, and placebo was conducted by Deurali-Janta Pharmaceuticals Pvt. Ltd" (page 17)
Allocation concealment (selection bias)	Unclear risk	Quote: "randomisation of spironolactone, acetazolamide, and placebo was conducted by Deurali-Janta Pharmaceuticals Pvt. Ltd" (page 17) Quote: "Three sealed master lists of the randomisation code were held by the manufacturer, an independent clinician at the Nepal International Clinic in Katmandu, and an independent clinician at the aid post in Pheriche (study enrolment location)." Page 17
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to score this item as low or high risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to score this item as low or high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Around 10% to 12% of participants were lost at follow-up
Selective reporting (reporting bias)	High risk	Outcomes important to participants, such as adverse events, were not reported
Other bias	Low risk	No other biases were identified

Wohns 1986

Methods	Design: parallel (2 arms) Country: China Multisite: no International: no Treatment duration: 7 to 10 days Follow-up: unclear Rate of ascent (m/h): unclear Final altitude reached: 5120 m AMS scale: "A modified general high altitude questionnaire was utilized to delineate and quantitative symptoms of acute mountain sickness. Twenty-two symptoms were listed as "yes"/"no" questions and rated on scales from 0, none; 1 to 3, slight; 4 to 6, moderate; and 7 to 9, extreme" Random unit: participants Analysis unit: groups
Participants	1. 21 participants enrolled (male climbers who normally reside at or near sea level. All were in excellent health and none ascended to altitudes over 14,500 feet for at least 1 month before participating in the study.) 21 participants randomized to: • phenytoin group (n = 9) • placebo group (n = 12) 2. No randomized patients were excluded from analysis 3. Participants lost at follow-up: none stated 4. Main characteristics of participants: • Age (mean/SD): ◦ Phenytoin group (35.5 ± 9.9) ◦ Placebo group (40 ± 11.4). • Number of men: ◦ Phenytoin group (n = 9) ◦ placebo group (n = 12) • History of AMS: ◦ phenytoin group (n = 5/9) 55% ◦ placebo group (n = 9/12) 75%
Interventions	Phenytoin group (intervention): no clear description provided Placebo group (control): no clear description provided
Outcomes	• Modified general high altitude questionnaire score • Risk of symptoms of AMS as moderate or severe headache and/or nausea Outcomes were not classified as primary or secondary
Notes	1. Trial Registration: not stated 2. Funder: United States Army Grant DAMD 17-84-G-4023 3. Role of funder: not stated 4. A priori sample size estimation: no 5. Conducted: not stated 6. Declared conflicts of interest: not reported 7. No contact information supplied in publication; unable to contact authors.

Wohns 1986 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to score this item as low or high risk of bias Quote "randomised clinical trial" (page 32)
Allocation concealment (selection bias)	Unclear risk	Insufficient information to score this item as low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to score this item as low or high risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to score this item as low or high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost at follow-up
Selective reporting (reporting bias)	High risk	Outcomes important to participants, such as adverse events, were not reported
Other bias	Low risk	No other biases were identified

ACTH = Adrenocorticotropic hormone; AMS = Acute Mountain Sickness; AMS-C = Acute Mountain Sickness score- cerebral subscale; AMS-R = Acute Mountain Sickness score- respiratory subscale; BP = Blood pressure; ESQ scores = Environmental Symptom Questionnaire; FVC= Forced vital capacity; g/dL = grams/decilitre; GHAQ = Generalized High Altitude Questionnaire; HACE = High altitude cerebral edema; HAH = High altitude headache; HAI = High altitude illness; HAPE = High altitude pulmonary oedema; ITT = Intention to treat; IV = Intravenous; kg = Kilograms; LLS = Lake Louise Scoring System; MAP = Mean artery pressure; mg = milligrams; NSAIDs = Nonsteroidal anti-inflammatory drugs; PASP = Pulmonary Artery Systolic Pressure; PEF = Peak expiratory flow; PH = degree of acidity or alkalinity of a solution; RCT = randomized controlled trial; SD = Standard deviation; SE = Standard error; SEM = standard error of the mean; VAS = Visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACME-1 2006	The study is focused on treatment of high altitude illness
Agostoni 2013	This study is not focused on prevention of high altitude illness

(*Continued*)

Bartsch 1993	The study is focused on treatment of high altitude illness
Bartsch 1994	The study is focused on treatment of high altitude illness
Bilo 2015	This study is not focused on prevention of high altitude illness
Bloch 2009	Non-randomized clinical trial
Broome 1994	The study is focused on treatment of high altitude illness
Cain 1966	This study is not focused on prevention of high altitude illness
Debevec 2015	This study is not focused on prevention of high altitude illness
Dumont 1999	This study is not focused on prevention of high altitude illness
Forster 1982	This study is not focused on prevention of high altitude illness
Forwand 1968	This study is not focused on prevention of high altitude illness
Fulco 2011	This study is not focused on prevention of high altitude illness
Gertsch 2002	This study is not focused on prevention of high altitude illness
Gray 1971	The study is focused on treatment of high altitude illness
Harris 2003	The study is focused on treatment of high altitude illness
Johnson 1988	This study is not focused on prevention of high altitude illness
Jonk 2007	This study is not focused on prevention of high altitude illness
Kotwal 2015	This study is not focused on prevention of high altitude illness
Lalande 2009	This study is not focused on prevention of high altitude illness
Lawley 2012	The study is focused on treatment of high altitude illness
Levine 1989	This study is not focused on prevention of high altitude illness
Liu 2013	This study is not focused on prevention of high altitude illness
Mairer 2012	This study is not focused on prevention of high altitude illness
McIntosh 1986	This study is not focused on prevention of high altitude illness

(*Continued*)

Purkayastha 1995	This study is not focused on prevention of high altitude illness
Reinhart 1994	This study is not focused on prevention of high altitude illness
Sandoval 2000	This study is not focused on prevention of high altitude illness
Scalzo 2015	This study is not focused on prevention of high altitude illness
Serra 2001	This study is not focused on prevention of high altitude illness
Siebenmann 2011	This study is not focused on prevention of high altitude illness
Singh 1969	The study is focused on treatment of high altitude illness
Solís 1984	This study is not focused on prevention of high altitude illness
Suh 2015	Non-randomized clinical trial
Teppema 2007	This study is not focused on prevention of high altitude illness
Vuyk 2006	This study is not focused on prevention of high altitude illness
White 1984	This study is not focused on prevention of high altitude illness
Wright 1988	This study is not focused on prevention of high altitude illness

Characteristics of studies awaiting assessment *[ordered by study ID]*

Dugas 1995

Methods	Double-blind randomized study
Participants	20 healthy volunteers received 5 mg of isradipine (n = 6) or placebo (n = 6) for 8 days. After 5 days of treatment in normoxia, the subjects were rapidly transported to an altitude of 4350 m
Interventions	Israpadine (calcium channel blocker) and placebo
Outcomes	AMS symptom score, haemodynamic parameters and renal function
Notes	Full text not available (January 2016)

Ellsworth 1987

Methods	Double-blind randomized study
Participants	47 climbers participated in this double-blind, randomized trial comparing acetazolamide 250 mg, dexamethasone 4 mg, and placebo every 8 hours as prophylaxis for acute mountain sickness during rapid, active ascent of Mount Rainier (elevation 4392 m). 42 subjects (89.4%) achieved the summit in an average of 34.5 hours after leaving sea level
Interventions	Acetazolamide 250 mg, dexamethasone 4 mg, and placebo every 8 hours
Outcomes	Acute mountain sickness, symptoms reported
Notes	Full text not available (January 2016)

Furian 2016

Methods	Double-blind randomized, placebo-controlled trial
Participants	112 people with COPD were studied in Bishkek (760 m), Kyrgyz Republic; and after travelling within 6 hours to Tuja Ashu clinic (3200 m) stayed there for 3 days
Interventions	Participants received dexamethasone (2 × 4 mg/d) or placebo before ascent and during stay at 3200 m
Outcomes	Cumulative risk of 1 of the following: AMS (AMSc environmental symptom cerebral score ≥ 0.7); severe hypoxaemia (SpO_2 < 75% for > 30 min); or discomfort requiring descent to low altitude
Notes	Full text not available (January 2017)

Hefti 2014

Methods	Double-blind, placebo-controlled trial
Participants	29 participants were assigned into a treatment group (14) receiving 800 IU vitamin E, 1000 mg vitamin C, 200,000 IU vitamin A, and 600 mg N-acetylcystein daily, starting 2 months prior to the expedition, and a placebo group (15)
Interventions	Vitamin group and placebo
Outcomes	AMS scores, Levels of endothelial micro particles
Notes	Full text not available (January 2016)

Kasic 1991

Methods	Randomized study
Participants	24 people who presented with acute mountain sickness
Interventions	A simulated descent of 1432 m (4600 ft) was attained by placing the participants in a fabric hypobaric chamber and pressurizing the chamber to 120 mm Hg above ambient pressure. Participants were randomly assigned to either the hypobaric treatment or treatment with 4 litres of oxygen given by facemask; both treatments lasted for 2 hours
Outcomes	Mean arterial oxygen saturation (SaO_2), symptoms of acute mountain sickness
Notes	Full text not available (January 2016)

Lee 2011

Methods	Randomized trial
Participants	Nineteen adolescents aged 13 to 18 years attempting an ascent of Mt. Kalapatar (5500 m)
Interventions	Acetazolamide, metazolamide
Outcomes	Risk of AMS, oxygen saturation and pulse rate
Notes	Full text not available (January 2017)

Pun 2014

Methods	Prospective double-blind placebo controlled randomized trial
Participants	358 pilgrims were recruited at Dhunche (1950 m) and followed up at Chandanbari (3350 m) and up to the sacred Lake Gosaikunda. Most of these pilgrims ascended from Dhunche to the lake in 2 to 3 days
Interventions	Low-dose acetazolamide (125 mg) and placebo
Outcomes	Lake Louise score (LLS) for AMS measurement, arterial oxygen saturation (SpO_2) and heart rate (HR)
Notes	Full text not available (January 2016)

Roncin 1996

Methods	Randomized trial
Participants	44 subjects were enrolled to participate in a study of the preventive effect of ginkgo biloba extract (EGb 761) on acute mountain sickness (AMS) and vasomotor changes of the extremities during a Himalayan expedition
Interventions	Ginkgo biloba extract (EGb 761) 160 mg and placebo
Outcomes	Environmental Symptom Questionnaire (ESQ) score and the cold gradient measured by photoplethysmograph

Roncin 1996 (*Continued*)

Notes	Full text not available (January 2016)

Swenson 1997

Methods	Randomized trial
Participants	19 healthy volunteers were assessed, who ingested in randomized order both a high carbohydrate (68% CHO) or normal carbohydrate (45% CHO) diet for 4 days. On the 4th day, subjects were exposed to 8 h of 10% normobaric oxygen
Interventions	High carbohydrate (68% CHO) or normal carbohydrate (45% CHO) diet for 4 days
Outcomes	Lake Louise Consensus Questionnaire, interleukins 1 beta, 6 and 8 (IL-1 beta, IL-6, IL-8) and tumour necrosis factor alpha (TNF-alpha)
Notes	Full text not available (January 2016)

Utz 1970

Methods	None known
Participants	None known
Interventions	None known
Outcomes	None known
Notes	Full text not available (January 2016)

Wang 1998

Methods	Randomized trial
Participants	65 men
Interventions	Conventional therapy group received oxygen, intravenous furosemide, aminophylline and dexamethasone; nifedipine group received oral nifedipine (10 mg, 3 × daily) in addition to conventional therapy; and participants in the nitric oxide group received nitric oxide (10 ppm) inhalation for 30 min, in addition to oral nifedipine
Outcomes	Pulmonary rales on auscultation and shadows on chest radiograph
Notes	Full text not available (January 2016)

Xiangjun 2014

Methods	Randomized trial
Participants	80 healthy young male plain residents (17 to 33 years old)
Interventions	Inhalation of budesonide (200 μg, twice daily), procaterol tablet (25 μg, twice daily), inhalation of budesonide/fomoterol (160 μg/4.5 μg, twice daily) or placebo (1 tablet, twice daily)
Outcomes	Lake Louis AMS questionnaire, blood pressure, heart rate, and oxygen saturation
Notes	Full text not available (January 2017)

AMS: Acute Mountain Sickness; CHO: Carbohydrate; EGb 761: Extract of Ginkgo biloba 761; ESQ: Environmental Symptom Questionnaire; HR: Heart rate; IL: Interleukin; LLS: Lake Louise score; mg: milligrams; min: minutes; ppm: parts per million; TNF: Tumour necrosis factor.

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-TRC-13003319

Trial name or title	Oral zolpidem for improving sleep and then prevention of acute mountain sickness: a single centre, randomised, double-blind, controlled, prospective trial
Methods	Interventional
Participants	Inclusion criteria 1. Aged between 18 and 35 years, including 18 and 35 years 2. People acutely ascending to high altitude. The gender ratio depends on actual situation 3. There is no history of plateau for a long time exposure 4. Before assessment, all subjects must be voluntary and sign a written informed consent Exclusion criteria 1. Recent history of taking sleeping pills 2. Engaged in specialized sports training 3. Subjects cannot take the drugs in our trial because of allergic history or other reasons 4. Subjects with bad compliance 5. Subjects with serious illnesses, e.g. sleep apnoea 6. Recent history of upper respiratory tract infection 7. The driver 8. Subjects with psychological or neurological disorder, and other conditions which are not appropriate for our trial Age minimum: 18 years old Age maximum: 35 years old Gender: both
Interventions	Experimental: oral zolpidem (10 mg, daily, oral) Control: oral placebo, the same dosage as oral zolpidem
Outcomes	Lake Louise Score

ChiCTR-TRC-13003319 (*Continued*)

Starting date	30 June 2013
Contact information	Huang Lan
Notes	Recruiting

ChiCTR-TRC-13003590

Trial name or title	The meaning of intravenous iron supplementation in acute mountain sickness: a randomised, double-blinded, placebo-controlled trial
Methods	Interventional
Participants	Inclusion criteria 1. Healthy subjects ready to travel from Beijing to Tibet by air 2. Subjects knowing the aim of the study and giving informed consent Exclusion criteria 1. Subject not finishing the procedure 2. Subject with coronary heart disease and uncontrolled hypertension and other severe diseases 3. Subject with anaemia especially iron deficiency anaemia Age minimum: 18 years old Age maximum: 65 years old Gender: both
Interventions	Intervention group: intravenous iron 200 mg Control: placebo
Outcomes	Serum iron; Lake Louise AMS score
Starting date	30 July 2013
Contact information	Ren Xuewen
Notes	Recruiting

NCT00886912

Trial name or title	Prevention of acute mountain sickness by intermittent hypoxic training
Methods	Interventional
Participants	Inclusion criteria 1. Healthy 2. Non-smoker 3. Endurance training minimum 2 times per week Exclusion criteria 1. Any diseases

NCT00886912 (*Continued*)

	2. Previous exposure to altitudes higher than 2000 m (last 6 weeks) Age minimum: 18 years old Age maximum: 55 years old Gender: both
Interventions	Other: hypoxia Other: normoxia
Outcomes	Risk of acute mountain sickness (time frame: after 20 hours at 4559 m) Severity of acute mountain sickness (time frame: after 20 hours at 4559 m)
Starting date	June 2008
Contact information	Kai Schommer, MD
Notes	Recruiting

NCT01606527

Trial name or title	Prospective, double-blind, randomized, placebo-controlled trial of ibuprofen versus placebo for prevention of neurologic forms of altitude sickness
Methods	Prospective, randomized, double-blind, placebo-controlled clinical trial evaluating ibuprofen and placebo for the prevention of neurological forms of altitude illness (including high altitude headache (HAH), acute mountain sickness (AMS), high altitude cerebral edema (HACE) and high altitude anxiety)
Participants	The study will take place in the spring and summer of 2012 at the Marine Corps Mountain Warfare Training Center in the Eastern Sierras near Bridgeport, California. US Marines from near sea level will participate in battalion-level training exercises at between 8500 and 11,500 feet, where some altitude illness is expected
Interventions	Ibuprofen 600 mg orally 3 times daily
Outcomes	1. Change in the risk of AMS as measured on the Lake Louise AMS Questionnaire across the study 2. Change in high altitude headache measured by the Visual Analog Scale (VAS) across the study 3. Change in cognitive performance as measured by King-Devick test across the study 4. Change in the presence of anxiety and somatic symptoms using the BSI-12 screening tool across the study 5. Change in the oxygen concentration using Pulse Oximetry across the study 6. Change in hydration status as measured by urine specific gravity across the study 7. Change in HAH risk and severity as measured on the Lake Louise AMS Questionnaire across the study 8. Change in cognitive performance as measured by the Quickstick across the study 9. Change in the presence of anxiety and somatic symptoms using the GAD-2 screening tool across the study 10. Risk of severe AMS as measured by a score of 6 or greater on the Lake Louise AMS Questionnaire
Starting date	July 2012
Contact information	Jeffrey Gertsch MD, Naval Health Research Center

NCT01606527 (*Continued*)

Notes	The recruitment status of this study is unknown. The completion date has passed and the status has not been verified in more than 2 years

NCT01682551

Trial name or title	Evaluation of the prevention and treatment effects of Chinese medicine on high altitude illness
Methods	Interventional
Participants	Inclusion criteria 1. Healthy adults Exclusion criteria 1. Chronic disease: cardiovascular disease, psychological disease, anaemia, migraine 2. Long-term use of the following materials: Chinese herbs, steroid, antibiotics 3. Altitude acclimation: have been to mountain over 2000 metres in the past 1 month 4. Pregnancy Age minimum: 20 years Age maximum: 70 years Gender: both
Interventions	Drug: acetazolamide Drug: Chinese medicine
Outcomes	Risk of acute mountain sickness will be measured by the Lake Louise Self Report (Lake Louise Score = 4 with headache) (time frame: the Lake Louise Score will be measured at noon of the second day after hiking to determine the onset of AMS) Arterial oxygen saturation (time frame: arterial oxygen saturation will be measured before and after the hike) Blood pressure (time frame: blood pressure will be measured before and after the hike) Heart rate (time frame: heart rate will be measured before and after the hike)
Starting date	September 2012
Contact information	Not stated
Notes	Not yet recruiting

NCT01794078

Trial name or title	A randomised, 4-sequence, double-blind study to test the safety of combined dosing with aminophylline and ambrisentan in exercising healthy human volunteers at simulated high altitude
Methods	Interventional
Participants	Inclusion criteria 1. Subjects must give written informed consent to participate in the study prior to undergoing any screening procedures. The subject will be given a signed and dated copy of the informed consent 2. Subjects must be healthy non-smoking (for 6 months or greater at commencement of Cycle 1) adult male

	and female volunteers; at least 18 through 50 years at screening, with a BMI of 18 kg/m² to 33 kg/m² and weighing at least 143 pounds (65 kg). Subjects' health status will be determined by the medical history, physical examination, vital signs, ECG, blood chemistry, haematology, and urinalysis performed at screening 3. Subjects must be willing to fast a minimum of 2 hours prior to screening 4. Subjects must be willing to abstain from alcohol and xanthine-containing food and beverages from 48 hours before check-in for each study day 5. Women who are of non-childbearing potential, must be: a) Surgically sterile (removal of both ovaries and/or uterus at least 12 months prior to dosing) and with an FSH level at screening of = 40 m IU/mL b) Naturally postmenopausal (spontaneous cessation of menses) for at least 24 consecutive months prior to dosing on Day 1, and with an FSH level at screening of 40 m IU/mL 6. Women of child-bearing potential must have a negative serum or urine pregnancy test at screening, during the study, and must agree to avoid pregnancy during study and for 3 months after the last dose of study drug. Pregnancy is tested at screening, during check-in of each testing cycle, during the follow-up visit, and at any given point if deemed necessary to the physician or designate. During treatment, women of child-bearing potential must use 2 acceptable methods of contraception at the same time unless the subject has had a documented tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS, in which case no additional contraception is required. Abstinence is not considered a form of contraception. Medically acceptable contraceptives include: (1) documented surgical sterilization (such as a hysterectomy), (2) barrier methods (such as a condom or diaphragm) used with a spermicide, or (3) an intrauterine device (IUD) or intrauterine system (IUS) 7. Male subjects must agree to take all necessary measures to avoid causing pregnancy in their sexual partners during the study and for 3 months after the last dose of study drug. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicidal. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use 8. Subjects must agree not to donate blood, platelets, or any other blood components 30 days, or plasma 90 days, prior to consenting and for 1 month after the last dose 9. Male subjects must agree not to donate sperm during the study and for 12 weeks after the last dose Exclusion criteria 1. Subjects with laboratory results outside the normal range, if considered clinically significant by the physician or delegate. In addition, subjects must have a haemoglobin concentration of = 12.0 g/dL 2. A mental capacity that is limited to the extent that the subject cannot provide legal consent or understand information regarding the side effects of the study drug 3. Currently abusing drugs or alcohol or with a history of drug or alcohol abuse within the past 2 years 4. Unwillingness or lack of ability to comply with the protocol, or to cooperate fully with the physician and site personnel 5. Use of any of the following: a) Any concomitant medication including oral contraceptive hormones. Subjects who have received any prescribed or non-prescribed (over-the-counter (OTC)) systemic medication, topical medications, or herbal supplements within 14 days from Day 1. St. John's Wort (hypericin) must not have been taken for at least 30 days prior to Cycle 1, Day 1 b) Any drugs, foods or substances known to be strong inhibitors or strong inducers of CYP enzymes (also known as cytochrome P450 enzymes) 6. Clinically significant ECG abnormality in the opinion of the physician or delegate 7. Vital signs or clinically significant laboratory values at the screening visit that in the opinion of the physician or delegate would make the subject an inappropriate candidate for the study 8. A VO_2 max value of less than 42 mL/kg/minute, as determined during exercise testing at screening. This

	value represents an educated estimate and may be changed, to include new information, at the discretion of the physician 9. A history of, or otherwise indicated predisposition for, claustrophobia, i.e. the fear of closed, narrow spaces (because of the limited size of the high altitude chamber) 10 A history of "undeserved" altitude sickness, i.e. altitude sickness at only moderate altitude. This would consist of altitude-related headaches, dizziness, or nausea during plane rides, or when travelling to moderately elevated locations of less than 9000 ft 11. Has taken any other investigational drug during the 30 days prior to the screening visit or is currently participating in another investigational drug clinical trial 12. Made any significant donation or have had a significant loss of blood within 30 days, or donated plasma within 90 days of consenting 13. Receipt of a transfusion or any blood products within 90 days prior to commencement of Cycle 1 14. History or manifestation of clinically significant neurological, gastrointestinal, renal, hepatic, cardiovascular, psychological, pulmonary, metabolic, endocrine, haematologic or other medical disorders. For the purpose of the study, individual fitness and health are more important than family history of disease burden as a criterion for participation. For example, an individual may have significant family history of cardiovascular disease; however, the individual subject's active lifestyle makes a manifestation of such disease at young ages unlikely. To account for such expected variation, the ultimate decision whether to exclude or include an individual based on family history or manifestation of disease will be made by the physician. The physician may choose to use physiological assessments, such as e.g. ECG, blood pressure, and VO^2 max fitness level as an aid for decision making 15. Any condition that might interfere Age minimum: 18 years old Age maximum: 50 years old Gender: both
Interventions	Drug: ambrisentan 5 mg Drug: aminophylline 400 mg
Outcomes	The safety of combined or single-dose aminophylline and ambrisentan at simulated altitude in exercising human subjects (time frame: safety endpoints will be measured during simulated high altitude (Cycle 2) at least 22 days post screening) The safety of combined or single-dose aminophylline and ambrisentan at simulated high altitude in resting human subjects (time frame: safety endpoints will be measured during an episode of simulated high altitude (Cycle 1), at least 7 days post screening)
Starting date	September 2013
Contact information	Claude A Piantadosi, MD
Notes	Active, not recruiting

NCT01993667

Trial name or title	Acetazolamide for the prevention of high altitude illness: a comparison of dosing
Methods	Interventional
Participants	Inclusion criteria 1. 18 years or older 2. English or Indian speaking 3. Mountaineers or trekkers who plan to climb Mt. McKinley or trek to Base Camp on Mt. Everest Exclusion criteria 1. Low sodium and/potassium blood serum levels 2. Kidney disease or dysfunction 3. Liver disease, dysfunction, or cirrhosis 4. Suprarenal gland failure or dysfunction 5. Hyperchloraemic acidoses 6. Angle-closure glaucoma 7. Taking high dose aspirin (over 325 mg/day) 8. Any reaction to sulfa drugs or acetazolamide 9. Pregnant or lactating women
Interventions	Drug: acetazolamide
Outcomes	Prevention of acute mountain sickness as measured by the Lake Louise Score (time frame: 1 year) Side effect profile of acetazolamide (time frame: 1 year)
Starting date	March 2012
Contact information	Scott McIntosh, MD
Notes	Recruiting

NCT02244437

Trial name or title	Ibuprofen vs acetaminophen in the prevention of acute mountain sickness: A double blind, randomised controlled trial
Methods	Interventional
Participants	Inclusion criteria: Healthy subjects between the ages of 18 and 65, male or female, non-Nepali, without AMS or any concurrent illness, and not already taking NSAIDs and acetazolamide or any other drug for the prevention of altitude illness Exclusion criteria: Individuals not meeting inclusion criteria, including mild AMS (more than 1 mild symptom on the Lake Louise Questionnaire) or significantly depressed oxygen saturation (< 75%); females known to be pregnant, cannot exclude the possibility of being pregnant, or have missed menses by over 7 days; individuals who have spent 24 hours at an altitude of 4500 metres/14,000 ft within the last 9 days; anyone known to have taken any of the following in the last 2 days: acetazolamide (Diamox®), steroids (dexamethasone, prednisone), theophylline, or diuretics (Lasix®); individuals who have a known intracranial space occupying lesion or a history of elevated intracranial pressure, (i.e. tumours, hydrocephalus, etc)

NCT02244437 (*Continued*)

	Age minimum: 18 years old Age maximum: 65 years old Gender: both
Interventions	Drug: acetaminophen Drug: ibuprofen
Outcomes	Diagnosis of Acute Mountain Sickness (AMS) (time frame: upon reaching 5000 m altitude (Lobuche) of Nepal Himalaya) Blood Oxygen Saturation (SPO_2) (time frame: upon reaching 5000 m altitude (Lobuche) of Nepal Himalaya) Heart Rate (HR) (time frame: upon reaching 5000 m altitude (Lobuche) of Nepal Himalaya) High Altitude Headache (HAH) (time frame: upon reaching 5000 m altitude (Lobuche) of Nepal Himalaya)
Starting date	October 2014
Contact information	Nicholas C Kanaan, MD
Notes	Active, not recruiting

NCT02450968

Trial name or title	Dexamethasone for prophylaxis of acute mountain sickness in patients with chronic obstructive pulmonary disease travelling to altitude
Methods	Interventional
Participants	Inclusion criteria: 1. Chronic obstructive pulmonary disease (COPD), GOLD criteria grade 1-2 2. Living at low altitude (< 800m) Exclusion criteria: 1. COPD exacerbation 2. severe COPD, GOLD grade 3 or 4 3. Arterial oxygen saturation < 92% at low altitude (< 800 metres) 4. Diabetes, uncontrolled cardiovascular disease such as systemic arterial hypertension, coronary artery disease; previous stroke; pneumothorax in the last 2 months 5. Untreated or symptomatic peptic ulcer disease, glaucoma, obstructive sleep apnoea 6. Internal, neurologic or psychiatric disease that interfere with protocol compliance including current heavy smoking (> 20 cigarettes per day) 7. Pregnant or nursing mothers Age minimum: 20 years old Age maximum: 75 years old Gender: both
Interventions	Drug: dexamethasone Drug: placebo
Outcomes	Acute mountain sickness, cumulative risk (time frame: day 3 at 3200 m) 6 minutes walk distance (time frame: day 2 at 3200 m) Acute mountain sickness, severity (time frame: day 1, day 2, day 3 at 3200 m)

NCT02450968 (*Continued*)

	Arterial blood gases (time frame: day 2 at 3200 m) Perceived exertion (time frame: day 2 at 3200 m)
Starting date	May 2015
Contact information	Talant M Sooronbaev, MD
Notes	Recruiting

NCT02604173

Trial name or title	A randomised controlled trial of altitude sickness prevention and efficacy of comparative treatments
Methods	Interventional
Participants	Inclusion criteria: 1. Male and Female 2. Sea level-dwelling hikers 3. Between ages 18 and 65 Exclusion criteria: 1. History of allergy to acetazolamide or budesonide (or other corticosteroids) 2. Taken NSAIDs, acetazolamide, or corticosteroids in the 1 week prior to study enrolment 3. Hazardous medical conditions which precludes the ability to moderately hike to high altitude including: sickle cell anaemia, asthma, or COPD, severe anaemia, or severe coronary arterial disease 4. Pregnancy or suspected pregnancy 5. Participants who are younger than 18 years of age and more than 65 6. Sleep above 4000 m elevation in the preceding 1 week 7. History of asthma or COPD 8. Current symptoms of an acute upper respiratory illness 9. Unable to complete a moderately strenuous hike at high altitude Age minimum: 18 years old Age maximum: 65 years old Gender: both
Interventions	Drug: acetazolamide Drug: budesonide Drug: placebo
Outcomes	Oxygen saturation (time frame: 24 hours) Pulmonary function testing - FEV1 (time frame: 24 hours) Pulmonary function testing - FVC (time frame: 24 hours) Pulmonary function testing - PEFR (time frame: 24 hours)
Starting date	August 2016
Contact information	Grant S Lipman, MD
Notes	Not yet recruiting

NCT02811016

Trial name or title	Effect of inhaled budesonide on the incidence and severity of acute mountain sickness at 4559 m
Methods	Prospective, controlled, single-centre study on 51 healthy volunteers at 4559 m
Participants	51 healthy volunteers
Interventions	Budesonide 200 µg inhaled at 7 a.m. and 7 p.m. Budesonide 800 µg inhaled at 7 a.m. and 7 p.m. Placebo inhalation at 7 a.m. and 7 p.m.
Outcomes	Assessment of risk and severity of acute mountain sickness by use of 2 internationally standardized and well-established questionnaires Venous (and capillary) blood drawings Transthoracic echocardiography for assessing pulmonary artery systolic pressure
Starting date	June 2016
Contact information	Marc Berger, Salzburger Landeskliniken
Notes	This study has been completed

NCT02941510

Trial name or title	Inhaled budesonide for altitude illness prevention
Methods	Randomized, double-blinded study administering budesonide, a medication to reduce inflammation in the lungs, to healthy volunteers to examine effects on altitude illness prevention by spending 18 hours overnight at 14,000 ft elevation
Participants	Participants will be recruited from the Denver community and prescreened for eligibility via phone. 100 participants, after consenting, will have baseline data and blood collected and will begin budesonide therapy 72 hours prior to being taken from Denver to Pikes Peak, where they will be observed at altitude for 18 hours. Participants will have the opportunity to withdraw consent at any time and will be monitored continuously by physician-researchers
Interventions	Budenoside; placebo
Outcomes	Primary Outcome Measures: 1. Changes in inflammation 2. Risk of Acute Mountain Sickness (AMS) 3. Changes in gene regulation
Starting date	April 2017
Contact information	University of Colorado, Denver
Notes	This study is not yet open for participant recruitment

AMS: Acute Mountain Sickness; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CYP: cytochrome P450 enzymes; dL: decilitre; ECG: electrocardiogram; FEV1: forced expiratory volume in 1 second; FSH: Follicle-stimulating hormone; ft: feet; FVC: forced expiratory vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease criteria; HAH: high altitude headache; HR: heart rate; kg: kilograms; IUD: Intrauterine device; IUS: Intrauterine system; LNG 20: levonorgestrel 20 μg/day; ml: millilitres; mg: milligrams; NSAIDs: Nonsteroidal anti-inflammatory drugs; OTC: over-the-counter; PEFR: peak expiratory flow rate ; TM: Morning-after pill; VO_2 : maximal oxygen consumption.

DATA AND ANALYSES

Comparison 1. Spironolactone: spironolactone vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk of acute mountain sickness	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

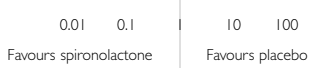
Analysis 1.1. Comparison 1 Spironolactone: spironolactone vs. placebo, Outcome 1 Risk of acute mountain sickness.

Review: Interventions for preventing high altitude illness: Part 2. Less commonly-used drugs

Comparison: 1 Spironolactone: spironolactone vs. placebo

Outcome: 1 Risk of acute mountain sickness

Study or subgroup	Spironolactone n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Brookfield 1977	2/6	5/6		0.40 [0.12, 1.31]
SPACE 2011	27/114	13/79		1.44 [0.79, 2.61]



APPENDICES

Appendix 1. Risk categories for acute mountain sickness

Risk categories	Description
Low	Individuals with no prior history of altitude illness and ascending to ≤ 2800 m/9186 feet.
Low	Individuals taking ≥ 2 days to arrive at 2500m to 3000 m/8202 feet to 9842 feet with subsequent increases in sleeping elevation < 500m by day/1640 feet by day
Moderate	Individuals with prior history of AMS and ascending to 2500m to 2800 m (8202 feet to 9186 feet) in 1 day.
Moderate	No history of AMS and ascending to > 2800 m (9186 feet) in 1 day
Moderate	All individuals ascending > 500 m/d (1640 feet) (increase in sleeping elevation) at altitudes above 3000 m/9842 feet.
High	History of AMS and ascending to ≥ 2800 m/9186 feet in 1 day
High	All individuals with a prior history of HAPE or HACE.
High	All individuals ascending to > 3500 m/11482 feet in 1 day.
High	All individuals ascending >500 m/1640 feet /d increase in sleeping elevation above > 3500 m/11482 feet.
High	Very rapid ascents (e.g. Mt Kilimanjaro).

Appendix 2. Medical terms glossary

Term	Definition	Source
Anorexia	The lack or loss of appetite accompanied by an aversion to food and the inability to eat	https://www.ncbi.nlm.nih.gov/mesh/68000855
Ataxia	Impairment of the ability to perform smoothly coordinated voluntary movements	https://www.ncbi.nlm.nih.gov/mesh/68001259
Dyspnoea	Difficult or laboured breathing.	https://www.ncbi.nlm.nih.gov/mesh/?term=Dyspnoea

(*Continued*)

Dizziness	An imprecise term which may refer to a sense of spatial disorientation, motion of the environment, or lightheadedness	https://www.ncbi.nlm.nih.gov/mesh/68004244
Endothelium	A layer of epithelium that lines the heart, blood vessels (endothelium vascular), lymph vessels (endothelium lymphatic), and the serous cavities of the body	https://www.ncbi.nlm.nih.gov/mesh/68004727
Fatigue	The state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli	https://www.ncbi.nlm.nih.gov/mesh/68005221
Hallucination	Subjectively experienced sensations in the absence of an appropriate stimulus, but which are regarded by the individual as real	https://www.ncbi.nlm.nih.gov/mesh/?term=Hallucination
Headache	The symptom of pain in the cranial region.	https://www.ncbi.nlm.nih.gov/mesh/68006261
Hernia	Protrusion of tissue, structure, or part of an organ through the bone, muscular tissue, or the membrane by which it is normally contained	https://www.ncbi.nlm.nih.gov/mesh/68006547
Hypoxia	A disorder characterized by a reduction of oxygen in the blood	https://www.ncbi.nlm.nih.gov/mesh/68000860
Insomnia	Disorders characterized by impairment of the ability to initiate or maintain sleep	https://www.ncbi.nlm.nih.gov/mesh/68007319
Lightheadedness	See dizziness.	
Nausea	An unpleasant sensation in the stomach usually accompanied by the urge to vomit	https://www.ncbi.nlm.nih.gov/mesh/68009325
Pulmonary oedema	Excessive accumulation of extravascular fluid in the lung, an indication of a serious underlying disease or disorder. Pulmonary oedema prevents efficient pulmonary gas exchange in the pulmonary alveoli, and can be life-threatening	https://www.ncbi.nlm.nih.gov/mesh/?term=Pulmonary+oedema
Pulmonary alveoli	Small polyhedral outpouchings along the walls of the alveolar sacs, alveolar ducts and terminal bronchioles through the walls of which gas exchange between alveolar air and pulmonary capillary blood takes place	https://www.ncbi.nlm.nih.gov/mesh/?term=Pulmonary+alveoli
Seizures	Clinical or subclinical disturbances of cortical function due to a sudden, abnormal, excessive, and disorganized discharge of brain cells. Clinical manifestations include	https://www.ncbi.nlm.nih.gov/mesh/68012640

(*Continued*)

	abnormal motor, sensory and psychic phenomena	

Appendix 3. The most frequents adverse events of the pharmacological interventions

Drug	Description and contraindications	Adverse events	Source
Acetazolamide	Acetazolamide, an inhibitor of the enzyme carbonic anhydrase Hypersensitivity to acetazolamide or any excipients in the formulation. Since acetazolamide is a sulphonamide derivative, cross-sensitivity between acetazolamide, sulphonamides and other sulphonamide derivatives is possible. Acetazolamide therapy is contraindicated in situations in which sodium and/or potassium blood serum levels are depressed, in cases of marked kidney and liver disease or dysfunction, in suprarenal gland failure, and in hyperchloraemic acidosis. It is contraindicated in patients with cirrhosis because of the risk of development of hepatic encephalopathy	Adverse reactions, occurring most often early in therapy, include paraesthesias, particularly a "tingling" feeling in the extremities, hearing dysfunction or tinnitus, loss of appetite, taste alteration and gastrointestinal disturbances such as nausea, vomiting and diarrhoea; polyuria, and occasional instances of drowsiness and confusion	DailyMed
Aspirin	It is a nonsteroidal anti-inflammatory drug	Reye's syndrome (a rare but serious illness). Stomach bleeding	DailyMed
Bosentan	It is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension Pregnancy, pre-existing hepatic impairment.	Elevations of liver aminotransferases (ALT, AST) and liver failure. Early liver injury may preclude future use as disease progresses Respiratory tract infection and anaemia	DailyMed
Dexamethasone	Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are	Several adverse events (e.g. hyperglycaemia, fluid retention, hypokalaemic alkalosis, potas-	DailyMed

(*Continued*)

	readily absorbed from the gastrointestinal tract. Glucocorticoids cause varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli. Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have sodium-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogues including dexamethasone are primarily used for their anti-inflammatory effects in disorders of many organ systems Contraindicated in systemic fungal infections	sium loss, sodium retention)	
Gabapentin	Gabapentin is an anticonvulsant. Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients	Somnolence, dizziness, ataxia, fatigue, and nystagmus.	DailyMed
Ginkgo biloba	This homeopathic product has not been evaluated by the Food and Drug Administration for safety or efficacy. FDA is not aware of scientific evidence to support homeopathy as effective	-	DailyMed
Methazolamide	Methazolamide is a potent inhibitor of carbonic anhydrase. Methazolamide therapy is contraindicated in situations in which sodium and/or potassium serum levels are depressed, in cases of marked kidney or liver disease or dysfunction, in adrenal gland failure, and in hyperchloraemic acidosis. In patients with cirrhosis, use may precipitate the development of hepatic encephalopathy	Adverse reactions, occurring most often early in therapy, include paraesthesias, particularly a "tingling" feeling in the extremities; hearing dysfunction or tinnitus; fatigue; malaise; loss of appetite; taste alteration; gastrointestinal disturbances such as nausea, vomiting, and diarrhoea; polyuria; and occasional instances of drowsiness and confusion	DailyMed

(*Continued*)

Nifedipine	It is a calcium channel blocker. Nifedipine must not be used in cases of cardiogenic shock. It is contraindicated in patients with a known hypersensitivity to any component of the tablet	Headache, flushing/heat sensation, dizziness, fatigue/asthenia, nausea	DailyMed
Phenytoin	Phenytoin sodium is an antiepileptic drug. Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins	Central nervous system (the most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion), gastrointestinal system (nausea, vomiting, constipation, toxic hepatitis, and liver damage)	DailyMed
Salmeterol	Long-acting beta2-adrenergic agonist. Contraindicated in patients with asthma. It should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension	It increases the risk of asthma-related death. Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia	DailyMed
Selective inhibitor of phosphodiesterase type 5 (taladafil and sildenafil)	It was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated	Headache and flushing.	DailyMed
Spironolactone	Aldactone oral tablets contain 25 mg, 50 mg, or 100 mg of the aldosterone antagonist spironolactone Aldactone is contraindicated for patients with anuria, acute renal insufficiency, significant impairment of renal excretory function, or hyperkalaemia	Gynecomastia and hyperkalaemia.	DailyMed

(*Continued*)

Sumatriptan	Sumatriptan is an agonist for a vascular 5-hydroxytryptamine (1) receptor subtype. It should not be given to patients with history, symptoms, or signs of ischemics cardiac, cerebrovascular, or peripheral vascular syndromes	Serious cardiac events, including some that have been fatal. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemias, myocardial infarction, ventricular tachycardia, and ventricular fibrillation	DailyMed
Theophylline	Theophylline is classified as a methylxanthine. Theophylline should be used with extreme caution in patients with the following clinical conditions due to the increased risk of exacerbation of the concurrent condition: active peptic ulcer disease, seizure disorders and cardiac arrhythmias (not including bradyarrhythmias)	Nausea, vomiting, headache, and insomnia.	DailyMed

Appendix 4. MEDLINE (Ovid SP) search strategy

1. exp Brain Edema/ or exp Pulmonary Edema/ or (?edema adj3 (high?altitude or cerebral or pulmonary)).mp. or ((mountain or high?altitude) adj3 (sickness or illness)).mp. or high?altitude.ti,ab.
2. exp Secondary Prevention/ or exp Primary Prevention/ or exp Drug Therapy/ or (drug therapy or prevent* or acclimati?ation or nifedipine or dexamethasone or taladafil or sildenafil or theophylline or salmeterol or acetazolamide or aspirin or sumatriptan or gabapentin or phenytoin or magnesium or ginkgo biloba or ascorbic acid or alpha-tocopherol acetate or alpha-lipoic acid or beta-carotene or selenium or zinc or bosentan or calcium channel blockers or selective inhibitor of phosphodiesterase type or nonsteroidal anti-inflammatory drug* or steroid* or glucocorticosteroid* or corticosteroid* or non-selective phosphodiesterase inhibitor* or carbonic anhydrase inhibitor* or beta agonist* or 5-HT1 receptor agonist* or N-methyl-D-aspartate antagonist* or antioxidant* or vitamin* or mineral* or endothelin antagonist*).mp.
3. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
4. 1 and 2 and 3

Appendix 5. Embase (Ovid SP) search strategy

1. brain edema/ or lung edema/ or (?edema adj3 (high?altitude or cerebral or pulmonary)).mp. or ((mountain or high?altitude) adj3 (sickness or illness)).ti,ab. or high?altitude.ti,ab.
2. secondary prevention/ or primary prevention/ or drug therapy/ or (drug therapy or prevent* or acclimati?ation or nifedipine or dexamethasone or taladafil or sildenafil or theophylline or salmeterol or acetazolamide or aspirin or sumatriptan or gabapentin or phenytoin or magnesium or ginkgo biloba or ascorbic acid or alpha-tocopherol acetate or alpha-lipoic acid or beta-carotene or selenium or zinc or bosentan or calcium channel blockers or selective inhibitor of phosphodiesterase type or nonsteroidal anti-inflammatory drug* or steroid* or glucocorticosteroid* or corticosteroid* or non-selective phosphodiesterase inhibitor* or carbonic anhydrase inhibitor* or beta agonist* or 5-HT1 receptor agonist* or N-methyl-D-aspartate antagonist* or antioxidant* or vitamin* or mineral* or endothelin antagonist*).ti,ab.
3. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab.) not (animals not (humans and animals)).sh.
4. 1 and 2 and 3

Appendix 6. CENTRAL search strategy

#1 MeSH descriptor Brain Edema explode all trees
#2 MeSH descriptor Pulmonary Edema explode all trees
#3 (?edema near (high?altitude or cerebral or pulmonary)) or ((mountain or high?altitude) near (sickness or illness)) or high?altitude:ti,ab
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Secondary Prevention explode all trees
#6 MeSH descriptor Primary Prevention explode all trees
#7 MeSH descriptor Drug Therapy explode all trees
#8 (drug therapy or prevent* or acclimati?ation or nifedipine or dexamethasone or taladafil or sildenafil or theophylline or salmeterol or acetazolamide or aspirin or sumatriptan or gabapentin or phenytoin or magnesium or ginkgo biloba or ascorbic acid or alpha-tocopherol acetate or alpha-lipoic acid or beta-carotene or selenium or zinc or bosentan or calcium channel blockers or selective inhibitor of phosphodiesterase type or nonsteroidal anti-inflammatory drug* or steroid* or glucocorticosteroid* or corticosteroid* or non-selective phosphodiesterase inhibitor* or carbonic anhydrase inhibitor* or beta agonist* or 5-HT1 receptor agonist* or N-methyl-D-aspartate antagonist* or antioxidant* or vitamin* or mineral* or endothelin antagonist*):ti,ab
#9 (#5 OR #6 OR #7 OR #8)
#10 #4 and #9

Appendix 7. Search strategy for LILACS via BIREME interface

"EDEMA CEREBRAL" or "edema pulmonary$" or "mountain sickness" or "high-altitude sickness" or "montaña enfermedad$" or "mal da montanha$" or "doença de alta altitude$" or "mal de altura$"

Appendix 8. WHO International Trials Registry Portal search

Advanced search
high-altitude pulmonary oedema (in the title field)

Appendix 9. Study eligibility screening and data extraction form

Intervention for preventing High altitude**illness**
Study Selection, Quality Assessment & Data Extraction Form

First author	Journal/Conference Proceedings etc	Year

Study eligibility

RCT/Quasi/CCT (delete as appropriate)	Relevant participants	Relevant interventions	Relevant outcomes
Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear	Yes / No* / Unclear

*** Issue relates to selective reporting when authors may have taken measurements for particular outcomes, but not reported these within the paper(s). Reviewers should contact trialists for information on possible non-reported outcomes & reasons for exclusion from publication. Study should be listed in 'Studies awaiting assessment' until clarified. If no clarification is received after three attempts, study should then be excluded.**

Do not proceed if any of the above answers are 'No'. If study to be included in 'Excluded studies' section of the review, record below the information to be inserted into 'Table of excluded studies'

Freehand space for comments on study design and treatment:

References to trial
Check other references identified in searches. If there are further references to this trial link the papers now & list below. All references to a trial should be linked under one *Study ID* in RevMan.

Code each paper	Author(s)	Journal/Conference Proceedings etc	Year
	The paper listed above		
	Further papers		

(*Continued*)

Participants and trial characteristics

Participant characteristics	
	Further details
Age (mean, median, range, etc)	
Sex of participants (numbers / %, etc)	
Country	
Other	
Rate of ascent (m/h)	
Final altitude reached (metres)	
AMS scale	
History of HAI	
Type of HAI reported	

Intervention characteristics

Intervention characteristics	
	Further details
Name	
Doses	
Administration route	
Time to administration	
Duration	

If RCT included a combination:

Intervention characteristics	
	Further details
Name	
Doses	
Administration route	
Time to administration	
Duration	

If RCT included acclimatization:

Intervention characteristics	
Rate of ascent (m/h)	Further details

Methodological quality

Allocation of intervention	
State here method used to generate allocation and reasons for grading	Grade (circle)
	Low risk of bias (Random)
	High risk of bias (e.g. alternate)
	Unclear

Concealment of allocation **Process used to prevent foreknowledge of group assignment in a RCT, which should be seen as distinct from blinding**	
State here method used to conceal allocation and reasons for grading	Grade (circle)
	Low risk of bias
	High risk of bias
	Unclear

Blinding	
Person responsible for participants care	Yes / No
Participant	Yes / No
Outcome assessor	Yes / No
Other (please specify)	Yes / No

Intention-to-treat
An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not

All participants entering trial
15% or fewer excluded
More than 15% excluded
Not analysed as 'intention-to-treat'
Unclear

Free selective report	
State here method used to generate allocation and reasons for grading	Grade (circle)
	Low risk of bias
	High risk of bias
	Unclear

Were withdrawals described? Yes ? No ? not clear ?

Discuss if appropriate

Data extraction

Outcomes relevant to your review Copy and paste from 'Types of outcome measures'	
	Reported in paper (circle)
risk of AMS (headache, nausea, insomnia, dizziness, and sleep disorder)	Yes / No
risk of HACE.	Yes / No
risk of HAPE.	Yes / No
Safety of adverse events	Yes / No
Safety (adverse drug reaction)	Yes / No

For Dichotomous data			
Code of paper	Outcomes	Intervention group (n) n = number of participants, not number of events	Control group (n) n = number of participants, not number of events
A	risk of AMS ((headache, nausea, insomnia, dizziness, and sleep disorder)		
	risk of HACE.		
	risk of HAPE		
	Safety of adverse events		
	Safety (adverse drug reaction)		

Other information which you feel is relevant to the results Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review

Freehand space for writing actions such as contact with study authors and changes

References to other trials

Did this report include any references to published reports of potentially eligible trials not already identified for this review?		
First author	Journal / Conference	Year of publication

Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, give list contact name and details

Trial characteristics	
	Further details
Single centre / multicentre	
Country / Countries	
How was participant eligibility defined?	
How many people were randomized?	
Number of participants in each intervention group	
Number of participants who received intended treatment	
Number of participants who were analysed	
Drug treatment(s) used	
Dose / frequency of administration	
Duration of treatment (State weeks / months, etc, if cross-over trial give length of time in each arm)	
Median (range) length of follow-up reported in this paper (state weeks, months or years or if not stated)	

(*Continued*)

Time-points when measurements were taken during the study	
Time-points reported in the study	
Time-points you are using in RevMan	
Trial design (e.g. parallel / cross-over*)	
Other	

Appendix 10. Assessment of risk of bias in included studies

We will assess the following domains as low risk of bias, unclear or high risk of bias:
Random sequence generation
Allocation concealment
Blinding (of participants, personnel and outcome assessors)
Incomplete outcome data
Selective reporting
Free of other bias (baseline imbalance, early stopping, academic fraud, drug company involvement) (Gurusamy 2009; Ioannidis 2008a; Ioannidis 2008b).
We will use the following definitions:

(1) Sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess the method as:

- Low risk (any truly random process, e.g. random number table; computer random number generator);
- High risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- Unclear , if the trial was described as randomized, but the method used for the allocation sequence generation was not described.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We will assess the methods as:

- Low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- High risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- Unclear , if the trial was described as randomized, but the method used to conceal the allocation was not described. .

(3) Blinding or masking (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will judge studies at low risk of bias if they were blinded, or if we judge that the lack of blinding could not have affected the results. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess the methods as:

- Low risk, High risk or unclear for participants;
- Low risk, High risk or unclear for personnel;
- Low risk , High risk or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, drop-outs, protocol deviations)

- Low risk, the numbers and reasons for drop-outs and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Unclear, the report gave the impression that there had been no drop-outs or withdrawals, but this was not specifically stated.
- High risk, the number or reasons for drop-outs and withdrawals were not described.

We will further examine the percentages of drop-outs overall in each trial and per randomization arm and we will evaluate whether intention-to-treat analysis has been performed or could be performed from the published information.

Were all randomized participants analysed in the group to which they were allocated? (intention-to-treat (ITT) analysis)

- Low risk of bias: specifically reported by authors that ITT was undertaken and this was confirmed on study assessment, or not stated but evident from study assessment that all randomized participants are reported/analysed in the group they were allocated to for the most important time point of outcome measurement irrespective of non-compliance and co-interventions.
- High risk of bias: lack of ITT confirmed on study assessment (patients who were randomized were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation) regardless of whether ITT reported or not.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; potentially inappropriate application of simple imputation.
- Unclear : described as ITT analysis, but unable to confirm on study assessment, or not reported and unable to confirm by study assessment.

(5) Selective reporting bias

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- Low risk(where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- High risk (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- Unclear: not all pre-defined, or clinically relevant and reasonably expected outcomes were reported on, or were not reported fully, or it was unclear whether data on these outcomes were recorded or not.

(6) Free of other bias

We will describe for each included study any important concerns we have about other possible sources of bias (Gurusamy 2009; Ioannidis 2008a; Ioannidis 2008b).

- Low risk of bias, the trial appears to be free of other components that could put it at risk of bias.
- Unclear, the trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias), there are other factors in the trial that could put it at risk of bias, e.g., no sample size calculation made, early stopping.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: AMC

Co-ordinating the review: AGG, AMC, IAR

Undertaking manual searches: VNE, DMF and IAR

Screening search results: AGG, DMF and IAR

Organizing retrieval of papers: AGG, DMF and IAR

Screening retrieved papers against inclusion criteria: VNE, DMF and IAR

Appraising quality of papers: VNE, DMF, AGG and IAR

Abstracting data from papers: VNE, DMF, AGG and IAR

Providing additional data about papers: VNE, DMF, AGG and IAR

Obtaining and screening data on unpublished studies: VNE, DMF, AGG and IAR

Data management for the review: IAR

Entering data into Review Manager 5 (RevMan 5) (Review Manager 2014): IAR

RevMan 5 statistical data: IAR and AMC

Other statistical analysis not using RevMan 5: AMC and IAR

Interpretation of data: VNE, DMF, AGG, AMC and IAR

Statistical inferences: VNE, DMF, AGG, AMC and IAR

Writing the review: VNE, DMF, AGG, AMC and IAR

Securing funding for the review: VNE, DMF, AGG, AMC and IAR

Guarantor for the review (one author): AGG

Person responsible for reading and checking review before submission: IAR

DECLARATIONS OF INTEREST

Alejandro Gonzalez Garay: nothing to declare.

Victor H Nieto Estrada: nothing to declare.

Daniel Molano Franco: nothing to declare.

Arturo Marti Carvajal: nothing to declare.

Ingrid Arevalo-Rodriguez: nothing to declare.

SOURCES OF SUPPORT

Internal sources

- Facultad de Ciencias de la Salud Eugenio Espejo, Universidad Tecnológica Equinoccial, Ecuador.
Academic.
- Methodology Research Unit/Neonatology, Instituto Nacional de Pediatria, Mexico.
Academic.

External sources

- Cochrane Anaesthesia Group, Denmark.
Academic.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Given that the original protocol was published in 2012, several sections needed updating to fulfil the current methodological guidelines for Cochrane Reviews (Higgins 2016).

We made the following changes to the published protocol (Martí-Carvajal 2012).

1. Considering the numerous interventions assessed for HAI prevention and on the recommendation of the ACE editors, we split the review into three parts. This current review is the second in a series of three, and focuses on less commonly used agents to prevent this condition. This change has implications in the title, scope and objective of this review and in the other reviews belonging to this series.

2. The Background was updated with new references to reflect current evidence about the target condition, as well as the scope on less commonly used interventions to prevent HAI.

3. The primary and secondary outcomes presented in the protocol - Martí-Carvajal 2012) - were modified to follow the MECIR guidelines (Higgins 2016), and improve their understanding. In particular, we made the following changes.

1. We removed 'All-cause mortality (by all causes or specific)' as a primary outcome of this review. This is because the risk of mortality is low in the general population, and it is not the primary goal for prevention.

2. We removed the outcome ' Combined incidence of AMS, HAPE or HACE (any of these alone or in combination)'. This is because this outcome is not often reported in studies, and this information can be easily calculated by the separate reporting of AMS, HAPE and HACE.

3. Previously the 'Risk of AMS' was a secondary outcome. It is a primary event to assess in prevention trials of HAI. We therefore moved this outcome from the list of secondary outcomes to the primary outcomes in this series of reviews. The risk of HAPE, HACE and adverse events are also important outcomes and they were included as secondary outcomes.

4. We included a new secondary outcome 'Difference in HAI/AMS scores at high altitude'. This is because it is frequently reported in studies, reflecting the severity of the disease

4. We limited the types of studies included to randomized controlled trials. We excluded quasi-randomized studies and prospective observational studies for evaluating clinical effectiveness, even if they reported adverse events. This was due to the high risk of bias involved in these types of studies.

5. We selected for this review five less commonly used types of interventions for the prevention of HAI. Other interventions will be addressed in the other two reviews belonging to this series.

6. Despite the fact that the protocol - Martí-Carvajal 2012 - did not include considerations about any unit of analysis, we identified one cross-over study for this review. It was included in our review to favour the full report of all evidence and it was analysed separately from parallel studies.

7. We stated in the protocol that we would contact trial authors in case of missing data or selective reporting (Martí-Carvajal 2012). However we were unable to undertake this task because in most cases no contact information was supplied in the publication.

8. We introduce several modifications in the Dealing with missing data section, in order to clarify the ITT analysis performed and to present the methods to impute missing information (mostly related to standard deviations).

9. Under Data synthesis we added a method named trial sequential analyses (TSA). However, due to the scarcity of data for the assessed comparisons in this review, and following the advice of ACE Editors, we decided not to report the TSA results in this case (all of them having only one study).

10. We also made extensive modifications to the Subgroup analysis and investigation of heterogeneity section, and we selected only three variables to analyse. However, we were unable to find information about significant pre-existing disease in included trials.

11. Due to scarcity of information we were not able to perform the planned sensitivity and subgroup analyses, as well as exploration of risk of reporting bias.

12. We used STATA 14 and the CS command to estimate the relative risk from individual studies. A method for this estimation was not included in the published protocol (Martí-Carvajal 2012).