Acetazolamide for the prevention of acute mountain sickness: a systematic review and meta-analysis

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ABSTRACT

Abstract

Background:

Acute mountain sickness (AMS) is a frequent complication among individuals ascending rapidly to high altitude and, if unrecognised or untreated, may progress to life-threatening high-altitude cerebral or pulmonary edema. Prophylactic pharmacotherapy is recommended for high-risk travellers, and acetazolamide is the most widely used agent. However, variability in trial designs and dosing regimens has led to ongoing uncertainty about the magnitude of benefit.

Objectives:

To evaluate the effectiveness of acetazolamide, compared with placebo, in preventing AMS in individuals ascending to high altitude.

Methods:

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing acetazolamide with placebo for AMS prevention. Electronic databases (PubMed, Ovid, Cochrane Library, Scopus and MEDLINE) were searched from inception to 2024 using the terms "acetazolamide", "acute mountain sickness" and "prevention". Studies enrolling participants at risk of AMS and reporting AMS incidence as a primary outcome were eligible. Duplicate publications and studies assessing only outcomes other than AMS prevention were excluded. Data were pooled as risk ratios (RRs) with 95% confidence intervals (CIs) using RevMan 5.4. Heterogeneity was quantified with the I^2 statistic. Risk of bias was assessed with the Cochrane Risk of Bias (RoB-1) tool and visualised using robvis.

Results:

From 184 records identified, 25 RCTs, including 2,433 participants, met eligibility criteria. Compared with placebo, acetazolamide significantly increased the proportion of participants who remained free of AMS (pooled RR for being AMS-free 1.20; 95% CI 1.12–1.29; $p < 0.00001$). Moderate statistical heterogeneity was observed ($I^2 = 54\%$; p for heterogeneity = 0.0008), indicating variability in effect estimates across trials, but the direction of effect consistently favoured acetazolamide.

Conclusions:

This meta-analysis of 25 randomized trials demonstrates that acetazolamide prophylaxis is effective in reducing the risk of AMS in individuals ascending to high altitude. In the absence of contraindications, acetazolamide should be considered as a key pharmacological strategy for AMS prevention in at-risk travellers, alongside gradual ascent and other non-pharmacological measures.

Keywords: *acute mountain sickness; acetazolamide; high altitude; prophylaxis; systematic review; meta-analysis*

INTRODUCTION

Acute mountain sickness (AMS) is a common clinical syndrome affecting non-acclimatised individuals who ascend rapidly to high altitude, typically above 2,500 m. It is characterised by headache, fatigue, dizziness, anorexia, nausea and disturbed sleep and can significantly impair function in trekkers, pilgrims, soldiers and workers at high altitude. [1,3] If unrecognised or inadequately managed, AMS may progress to high-altitude cerebral edema (HACE) or high-altitude pulmonary edema (HAPE), both of which are potentially fatal. [1]

Current prevention strategies for AMS emphasise graded ascent, rest days for acclimatisation and adequate hydration. However, these measures are often constrained by logistical or operational demands (for example, military deployment, labour requirements or fixed commercial trekking itineraries). In such contexts, chemoprophylaxis becomes an important adjunct.

Acetazolamide, a carbonic anhydrase inhibitor, induces a mild metabolic acidosis, thereby increasing ventilatory drive and improving oxygenation at altitude. [2,3] It also promotes diuresis and may modulate cerebrospinal fluid production, further contributing to its beneficial effects in altitude illnesses. Acetazolamide has long been recommended in clinical practice guidelines for AMS prevention, yet trial-level evidence has been heterogeneous in terms of dose, timing of initiation, ascent profile and outcome definitions.

Several individual randomized trials have suggested a protective effect of acetazolamide, but sample sizes were often modest, and estimates imprecise. In addition, the evidence base spans several decades, during which diagnostic criteria for AMS and ascent practices have evolved. [1–3] An updated synthesis using contemporary systematic review methods is therefore warranted.

The objective of this systematic review and meta-analysis was to evaluate the effectiveness of acetazolamide, compared with placebo, in preventing AMS among individuals ascending to high altitude.

METHODS

Protocol and registration

The protocol for this systematic review and meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration ID: CRD42024607776). The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.

Eligibility criteria

We included studies that met the following criteria:

• Study design: randomized or quasi-randomized controlled trials.

• Population: individuals (of any sex or age group) at risk of AMS due to rapid ascent to high altitude.

• Intervention: acetazolamide administered as prophylaxis before or during ascent, at any dose or regimen.

• Comparator: placebo or matching control without active pharmacological prophylaxis.

• Outcome: incidence (or prevention) of AMS reported as a primary or major secondary outcome, using any recognised diagnostic criteria (e.g., Lake Louise Score).

• Setting: any high-altitude environment (trekking, mountaineering, military deployment, occupational exposure, or simulated altitude).

We excluded non-randomized studies, trials where acetazolamide was used solely as treatment rather than prophylaxis, and studies that did not report AMS prevention or incidence as an outcome. Duplicate publications were identified and removed.

Information sources and search strategy

A comprehensive literature search was performed in PubMed, Ovid, the Cochrane Library, Scopus and MEDLINE, from database inception to 2024. The main search terms were "acetazolamide", "acute mountain sickness" and "prevention", combined with Boolean operators. Reference lists of key reviews and eligible trials were screened for additional studies.

No language restrictions were explicitly applied at the search stage. Where necessary, non-English articles were screened using translated abstracts and, if potentially eligible, assessed in more detail.

Study selection

All titles and abstracts retrieved from the searches were screened to exclude clearly irrelevant studies. Full-text articles were then obtained for potentially eligible records and assessed against the inclusion and exclusion criteria. Disagreements were resolved by discussion among the reviewers.

In total, 184 records were identified, of which 25 randomized trials[4-27] met the inclusion criteria and were included in the final quantitative synthesis.

Data extraction

For each eligible study, the following information was extracted where available: Study characteristics (year, setting, type of ascent), Participant characteristics (sample size, baseline demographics), Details of the intervention (acetazolamide dose, timing of initiation, duration), Comparator details (placebo characteristics), Definitions and diagnostic criteria used for AMS, Number of participants with and without AMS in each treatment arm

Data were extracted independently by reviewers using a standardised data collection form. Any discrepancies were resolved through consensus.

Risk of bias assessment

Risk of bias for each included trial was assessed using the Cochrane Risk of Bias version 1 (RoB-1) tool, covering the domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias. The robvis tool was used to generate risk-of-bias traffic and summary plots.

Summary measures and statistical analysis

The primary effect measure was the risk ratio (RR) for remaining free of AMS (i.e., AMS prevention) in the acetazolamide group compared with the placebo group. Categorical data were pooled using the risk ratio with corresponding 95% confidence intervals (CIs). Meta-analysis was conducted using RevMan 5.4 software.

Statistical heterogeneity among studies was evaluated using the chi-square test (Cochran's Q) and quantified with the I^2 statistic. An I^2 value of 50–75% was interpreted as moderate heterogeneity. Where heterogeneity was present, potential sources were explored qualitatively.

Given that this review synthesised aggregated data from previously published trials, formal ethics committee approval and informed consent were not required.

RESULTS

Study selection (Fig 1)

The database search yielded 184 records. After removal of duplicates and screening of titles and abstracts, full texts were obtained for studies that potentially met the inclusion criteria. Twenty-five randomized controlled trials, enrolling a total of 2,433 participants, were included in the final meta-analysis.

Characteristics of included studies (Table 1)

The included trials evaluated acetazolamide prophylaxis in a variety of altitude exposure contexts, including mountaineering expeditions, trekking itineraries and other high-altitude environments. Across studies, acetazolamide was administered before or during ascent, and compared with placebo. AMS was diagnosed using recognised clinical criteria; however, the exact definitions and thresholds varied between trials, contributing to clinical heterogeneity.

Risk of bias (Fig 2)

Overall, study quality was variable. Random sequence generation and allocation concealment were adequately described in some, but not all, trials. Blinding of participants and outcome assessors was generally attempted through the use of matching placebos, although details were not uniformly reported. Incomplete outcome data and selective reporting were infrequently judged as major concerns, but several trials had domains rated as "unclear" due to insufficient methodological information.

Effect of acetazolamide on prevention of AMS (Fig 3)

Pooled analysis of the 25 RCTs showed that acetazolamide significantly improved AMS prevention compared with placebo. Expressed as the proportion of participants remaining free of AMS, the overall RR was 1.20 (95% CI 1.12–1.29; $p < 0.00001$), favouring acetazolamide. In practical terms, this indicates that individuals receiving acetazolamide had a 20% higher likelihood of remaining free from AMS than those receiving placebo.

Moderate heterogeneity was observed among the included trials ($I^2 = 54\%$; p for heterogeneity = 0.0008). Despite this heterogeneity in effect sizes, the direction of effect consistently favoured acetazolamide in the majority of studies, and there was no suggestion that acetazolamide increased the risk of AMS in any setting.

Formal subgroup analyses (for example by dose, timing of initiation or ascent profile) were not reported in detail in the poster dataset, and could therefore not be robustly reproduced here. Nevertheless, the overall pattern suggests a class effect across a range of regimens and exposure conditions.

FIGURES AND IMAGES

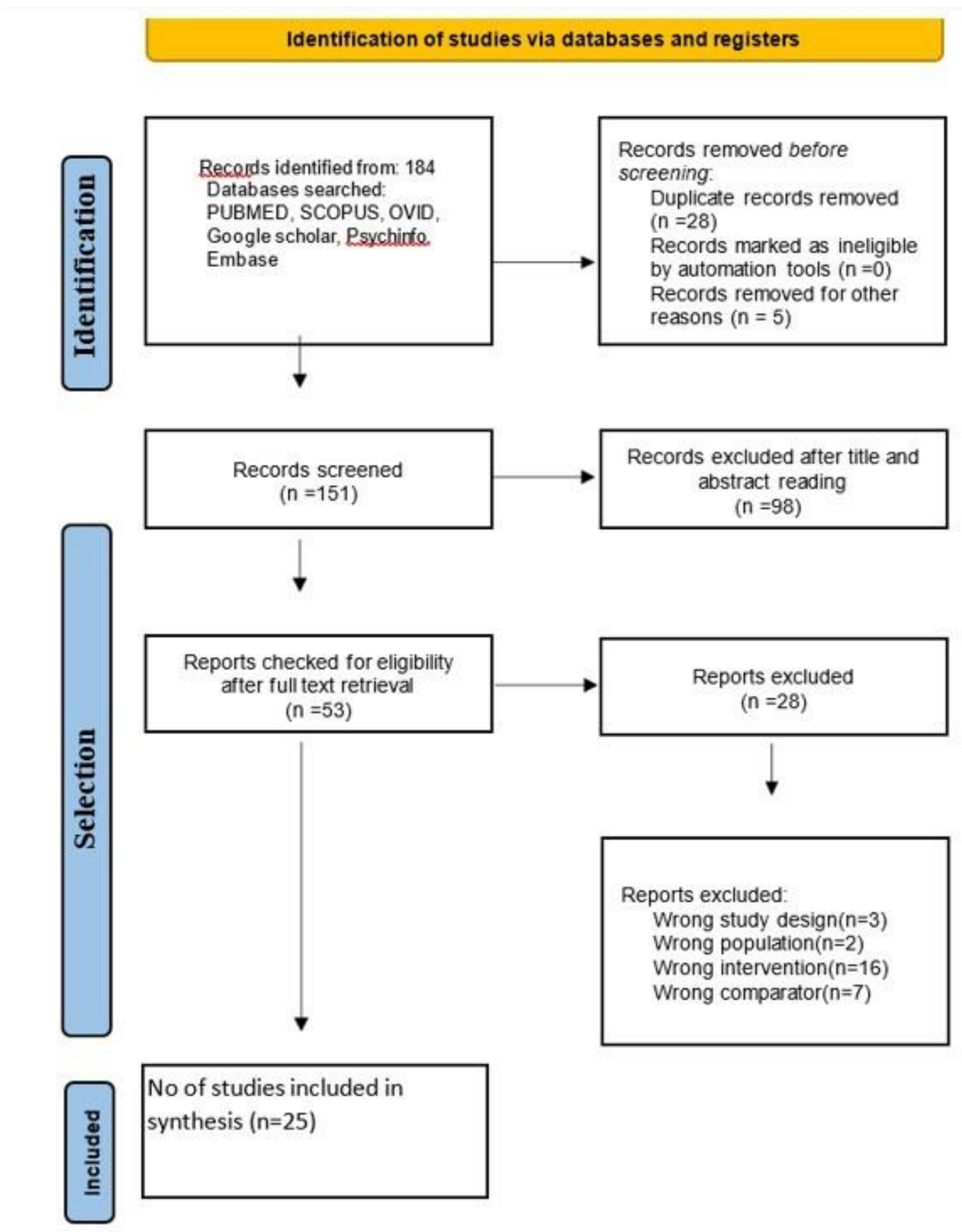

Fig 1: PRISMA flow diagram showing the identification, screening, eligibility assessment and final inclusion of 25 studies from 184 records identified in the literature search.

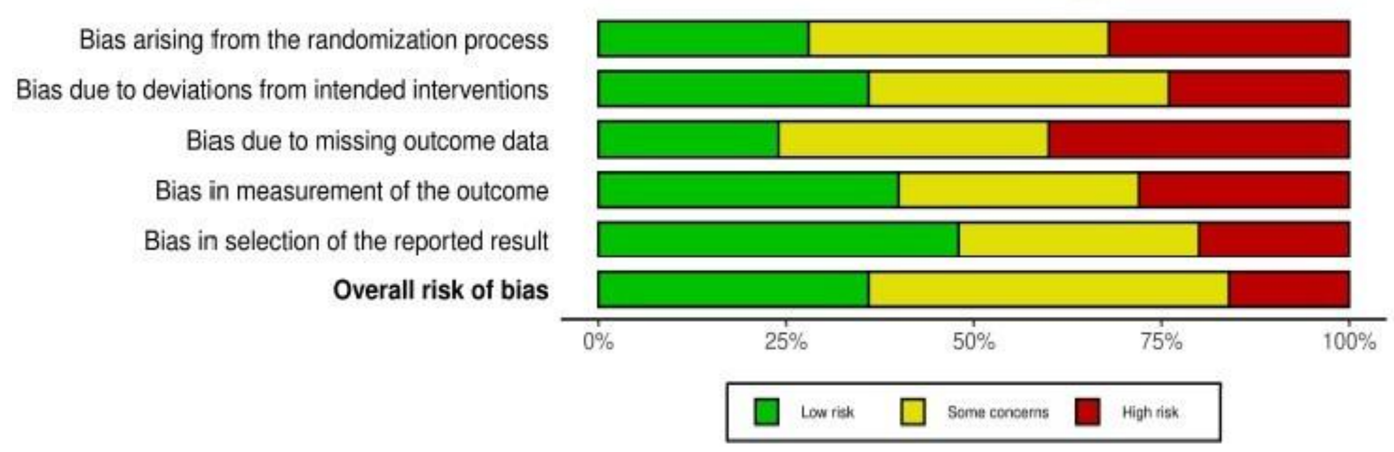

Fig 2: Summary of risk-of-bias assessment across included studies showing proportions rated as low risk, some concerns, or high risk for each bias domain.

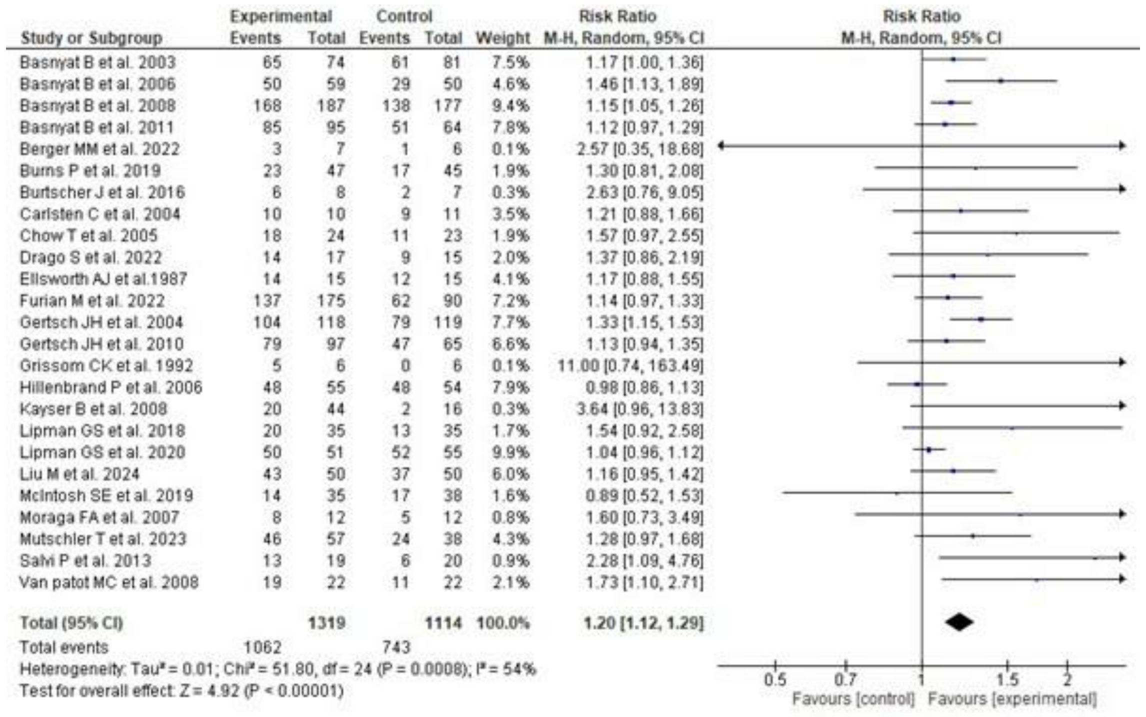

Fig3: Forest plot showing the pooled effect of acetazolamide versus control for prevention of acute mountain sickness across included randomized studies

TABLES

Table 1: Table showing key characteristics of the clinical studies included in the meta-analysis evaluating acetazolamide for prevention of acute mountain sickness.

No.	Study	Participants & setting	Study design	Intervention vs comparator(s)	Outcomes used in meta-analysis
1	Lipman 2018	Healthy adults, rapid ascent to 3810 m (White Mountain, USA)	Randomised, dbl-blind, 3-arm field RCT	Aza 125 mg BID vs inhaled budesonide vs placebo	AMS incidence at 3810 m (LLS ≥3 incl. headache)
2	Drago 2022	Healthy adults, 2-day climb to 4950 m (Mt Leoneras, ~4950 m)	Randomised, open-label non-inferiority	Aza 250 mg BID vs voluntary hyperventilation (no drug)	AMS at high camp/summit (LLS ≥3 with headache)
3	Lipman 2020	Healthy adults, rapid ascent to 3810 m	Randomised, dbl-blind, active-control	Aza 62.5 mg BID vs 125 mg BID	AMS incidence at altitude (LLS-based)
4	Kayser 2008	Trekkers on Mt Kilimanjaro (~5895 m)	Randomised, dbl-blind RCT (ASA analogue vs placebo) + non-rand Aza cohort	Calcium carbasalate 400 mg BID vs placebo; separate Aza ≈250 mg BID cohort	AMS during ascent (LLS)
5	Liu 2024	Healthy lowlanders, hypoxia lab (≈4000 m, 6 h)	Randomised, parallel-group clinical trial	Aza 125 mg BID ± remote ischaemic preconditioning vs RIPC alone vs control	AMS during 6-h hypoxic exposure (LLS / AMS-C)
6	Chow 2005	Healthy adults, rapid transport to ≈3800 m	Randomised, dbl-blind, 3-arm RCT	Aza 125 mg BID vs ginkgo 60 mg TID vs placebo	AMS at altitude (LLS ≥3 with headache)
7	Ellsworth 1987	Recreational climbers on Mt Rainier (~4390 m)	Randomised, dbl-blind, 3-arm field RCT	Aza 250 mg q8h vs dexamethasone 4 mg q8h vs placebo	AMS symptoms during climb / at summit
8	Basnyat 2011	Part-acclimatised trekkers, Everest region (4300→5000 m)	Randomised, dbl-blind, 3-arm RCT	Aza 250 mg BID vs spironolactone 50 mg BID vs placebo	AMS incidence on subsequent trekking days (LLS)
9	Grissom 1992	Patients with established AMS at high-altitude resort	Randomised, dbl-blind treatment trial	Therapeutic Aza ≈750 mg/day vs placebo after AMS diagnosis	Change in AMS symptoms and gas exchange over 24 48 h
10	Hillenbrand 2006	Nepali porters, Namche 3440→Lobuche 4930 m	Randomised, dbl-blind, placebo-controlled	Aza 250 mg OD vs placebo from 3440 m	AMS scores and incidence at higher camps (LLS)
11	Gertsch 2004	Western trekkers 4280→4928 m, Everest region	Randomised, dbl-blind, 4-arm RCT	Aza 250 mg BID vs ginkgo 60 mg BID vs combo vs placebo	AMS incidence during trek (LLS)
12	Berger 2022	HAPE susceptible lowlanders 1130→4559 m (Swiss Alps)	Randomised, dbl-blind, placebo-controlled	Aza 250 mg TID vs placebo from 48 h pre-ascent	Pulmonary artery pressure, HAPE; AMS (LLS) secondary
13	Burns 2019	Adults ascending to 3810 m (White Mountain)	Randomised, dbl-blind, non-inferiority	Aza 125 mg BID vs ibuprofen 600 mg TID	Altitude sickness / AMS incidence (LLQ)
14	van Patot 2008	Healthy lowlanders 1600→4300 m (Colorado)	Randomised, dbl-blind, placebo-controlled	Aza 125 mg BID x3 days pre ascent & at altitude vs placebo	AMS incidence/severity first 24 h at 4300 m (LLS / AMS-C)
15	Basnyat 2006	Trekkers 3440→4928 m, Everest (PACE Trial)	Randomised, dbl-blind, 3-arm RCT	Aza 125 mg BID vs 375 mg BID vs placebo	AMS during trek (LLS), dose-response + side-effects
16	Basnyat 2003	Trekkers 4243→4937 m, Everest region	Randomised, dbl-blind, placebo-controlled	Aza 125 mg BID vs placebo from 4243 m	AMS incidence at 4937 m (LLS ≥3 with headache)
17	Moraga 2007	People ascending to 3696 m (Ollagüe, Chile)	Randomised, placebo-controlled	Ginkgo vs placebo (no Aza)	AMS incidence at 3696 m (LLS)
18	Furian 2022 (NEJM Evid.)	COPD + healthy adults, ~700→2590 3100 m	Randomised, dbl-blind, placebo-controlled	Aza ≈125 mg TID vs placebo pre- and at altitude	Composite altitude-related adverse effects incl. AMS
20	Carlsten 2004	Tourists at 3630 m high-altitude resort	Randomised, dbl-blind, multi-arm dose-response RCT	Aza 125 mg BID vs 250 mg BID vs placebo	AMS symptoms and incidence over first day at 3630 m
21	Gertsch 2010 (HEAT)	Trekkers/climbers at high altitude	Randomised, dbl-blind, 3-arm RCT	Aza (≈125 mg BID) vs ibuprofen 600 mg TID vs placebo	High-altitude headache primary; AMS secondary
22	Salvi 2013	Healthy volunteers at ≈3500 4500 m	Randomised physiological trial	Aza (moderate dose) vs placebo/no Aza	Subendocardial viability ratio; AMS secondary, if present
23	McIntosh 2019 (RADICAL)	Trekkers/climbers to high altitude	Randomised, dbl-blind, non-inferiority	Aza 62.5 mg BID vs 125 mg BID	Altitude illness / AMS incidence; side-effects
24	Basnyat 2008	Trekkers 4250/4350→5000 m, Everest region	Randomised, dbl-blind, placebo-controlled	Aza (std prophylactic dose) vs placebo at high altitude	Pulmonary artery pressure primary; AMS secondary
25	Burtscher 2016	Lowlanders 500 600→3480 m (Alps)	Randomised, placebo-controlled field trial	Aza 125 mg BID from 1 day pre-ascent vs placebo	Systemic BP & SpO_2 during exercise; AMS secondary
26	Mutschler 2024	Lowlanders ≥40 yrs 760→3100 m (Swiss Alps)	Randomised, placebo-controlled	Aza (≈125 mg TID) vs placebo pre- and at altitude	Postural control primary; AMS incidence secondary

Table 1: Table showing key characteristics of the clinical studies included in the meta-analysis evaluating acetazolamide for prevention of acute mountain sickness.

DISCUSSION

In this systematic review and meta-analysis of 25 randomized trials including 2,433 participants, acetazolamide prophylaxis significantly incAreceataszeodlatmhiedepimoApcourteioMnouonftaiinndSiivcikdnuesalsPrevention who remained free from AMS compared with placebo. The pooled effect size (RR 1.20; 95% CI 1.12–1.29) indicates a clinically relevant benefit in high-risk travellers ascending to altitude.

Comparison with existing knowledge

The findings of this quantitative synthesis are in line with established clinical experience and pathophysiological rationale. Acetazolamide enhances ventilatory drive through induction of a mild metabolic acidosis and may reduce symptoms by improving arterial oxygenation and modulating cerebrospinal fluid dynamics.[2,3] Previous narrative reviews and clinical guidelines have recommended acetazolamide as first-line pharmacologic prophylaxis for AMS, but have often relied on smaller subsets of trials or older evidence bases.[1–3] By pooling 25 RCTs, this meta-analysis provides more precise and contemporary estimates of benefit.

Heterogeneity and methodological considerations

Moderate heterogeneity ($I^2 = 54\%$) was observed, reflecting differences in study design, acetazolamide dosing regimens, timing and rate of ascent, baseline risk of AMS, and diagnostic criteria across trials. Such heterogeneity is expected in altitude medicine research, where operational constraints frequently shape study protocols.

Rather than undermining the conclusions, this heterogeneity may actually strengthen the external validity of the findings: acetazolamide demonstrated benefit across a broad spectrum of real-world ascent profiles and participant populations. However, it limits our ability to recommend a single "optimal" dose or regimen based solely on these pooled data.

Risk-of-bias assessment suggested that, while many trials attempted appropriate randomisation and blinding, reporting was often incomplete, especially in older studies. This introduces some uncertainty about the magnitude of effect, but the consistent direction of benefit across trials and the highly significant pooled estimate make substantial bias in favour of acetazolamide less likely.

From a clinical and operational standpoint, these results support the use of acetazolamide as a core pharmacological strategy for AMS prevention in individuals at moderate-to-high risk, such as travellers following rapid ascent itineraries (for example, commercial treks with limited acclimatisation days), military personnel or workers who must ascend quickly for operational reasons, and people with a prior history of AMS or other recognised risk factors.

Acetazolamide should not be viewed as a substitute for gradual ascent and appropriate acclimatisation, which remain the cornerstones of AMS prevention. Instead, it should be integrated into a comprehensive strategy that includes itinerary planning, education on symptom recognition and access to descent or supplemental oxygen where feasible.

The choice of dose, timing of initiation and duration of prophylaxis should be individualised, taking into account patient comorbidities, contraindications (e.g., sulfonamide hypersensitivity, significant renal or hepatic impairment) and local practice patterns. Many commonly used regimens in practice (e.g., divided doses initiated one or two days before ascent) are consistent with those evaluated in the included trials, though dose-specific conclusions cannot be drawn from the summary data used here

CONCLUSION

This systematic review and meta-analysis demonstrates that acetazolamide prophylaxis significantly improves prevention of acute mountain sickness compared with placebo among individuals ascending to high altitude. Despite moderate heterogeneity across trials, the direction of effect is consistent and clinically meaningful.

In appropriate candidates, acetazolamide should be considered an important component of AMS prevention, in conjunction with non-pharmacological strategies such as gradual ascent and adequate acclimatisation. Clear counselling on potential adverse effects and contraindications remains essential.

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