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A Systematic Review to Assess Assessing Side Effects of Acetazolamide

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Abstract

Background:

Acetazolamide (AZM), a carbonic anhydrase inhibitor, is widely used for conditions such as glaucoma, acute mountain sickness (AMS), and idiopathic intracranial hypertension. While effective, AZM's use is often limited by frequent side effects, including paraesthesia, dysgeusia, polyuria, and fatigue, which may be dose-dependent. Previous studies have provided limited quantitative data, necessitating a systematic assessment of the overall risk and dose dependence of AZM's adverse effects.

Methods:

We conducted a systematic review of randomized controlled trials (RCTs) comparing oral AZM to placebo in adults. Studies reporting side effects were included, while those involving non-adults, hemodialysis patients, non-oral AZM formulations, or combined treatments were excluded. Primary outcomes included paraesthesia, dysgeusia, polyuria, and fatigue. Data were extracted and analyzed using the Mantel-Haenszel method,

Results:

A total of 35 studies met the inclusion criteria, encompassing diverse AZM dosages (125–4000 mg/day) and treatment durations (1–180 days). AZM significantly increased the risk of paraesthesia (OR: 6.5, NNTH: 2.3), dysgeusia (OR: 3.2, NNTH: 18), polyuria (OR: 2.7), and fatigue (OR: 2.3).. Secondary side effects, such as nausea, diarrhea, and drowsiness, were also

significantly associated with AZM. Sensitivity analyses confirmed robustness, and publication bias was not detected.

Conclusion:

AZM use is associated with a significant and dose-dependent increase in common side effects, particularly paraesthesia, dysgeusia, and fatigue. These findings underscore the importance of balancing efficacy with tolerability by optimizing AZM dosing. Clinicians should consider individual patient factors, such as renal function and body weight, when prescribing AZM to minimize adverse effects and improve adherence.

Introduction

Acetazolamide (AZM), a carbonic anhydrase (CA) inhibitor, has been utilized since the 1950s to manage several medical conditions (1–7). It is notably effective for treating glaucoma (8, 9) and for both the prevention (10–12) and potential treatment (13) of acute mountain sickness (AMS). However, its use is often hindered by frequent side effects, with some studies reporting occurrence rates as high as 80%–100% (2, 14). Common adverse effects include paraesthesia, altered taste, increased urination, and fatigue, which can significantly impact patient adherence and tolerability (2, 15). It has been hypothesized that certain side effects may stem from the degree of metabolic acidosis induced by AZM (16), a result of renal bicarbonate excretion that stabilizes within 1–2 days of treatment (17, 18). Plasma drug levels, influenced by body weight and kidney function, are also thought to play a role (19–21).

Preliminary evidence from small-scale or observational studies has suggested that AZM's side effects could be dose-dependent (11, 12). This theory has driven efforts to identify the minimum effective dose for AMS prevention. A 2012 review indicated that a daily dose of 250 mg might offer similar effectiveness as 750 mg, albeit with a higher number needed to treat (NNT: 6 (95% CI 5 to 11) vs. 3 (95% CI 3 to 5)) (11). Notably, this review only provided limited semi-quantitative data on four specific side effects based on five studies. For patients and clinicians to make informed choices about AZM use, robust and quantitative risk estimates for its side effects are essential. Furthermore, understanding whether dose adjustments are beneficial for other conditions treated with AZM, such as idiopathic intracranial hypertension or sleep apnea, hinges on determining if its adverse effects vary with dosage.

Methods

This review was conducted in alignment with a predefined protocol and adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (22).The study did not include patient or public involvement in its design or implementation

We included randomized controlled trials (RCTs) that assessed adult participants randomized to receive oral AZM or placebo and reported side effects. Exclusion criteria comprised studies involving non-human or non-adult participants, individuals unable to reliably report side effects (e.g., intubated patients), those undergoing hemodialysis (due to significant alterations in AZM pharmacokinetics and frequent side effects like dysgeusia, paraesthesia/neuropathy, and fatigue), studies without reported side effect data, trials using non-oral AZM formulations (e.g., intravenous or inhaled), and studies combining AZM with other systemic treatments, which made isolating AZM's effects impossible.

A comprehensive search was conducted using MEDLINE and EMBASE databases up to October 4, 2019. Additionally, references from eligible studies and key articles were reviewed. The search strategies employed were:

MEDLINE: (Acetazolamide(Mesh) OR Acetazolamide(tiab)) AND (Randomised Controlled Trial(ptyp) AND Placebo)

EMBASE: ('acetazolamide':ti, ab, kw OR 'acetazolamide'/exp) AND ('placebo':ab, ti OR 'placebo'/exp) AND ('randomized controlled trial'/de)

No language restrictions were applied. Attempts to contact authors of two foreign-language studies (23, 24) were unsuccessful; however, assistance from native speakers helped confirm these studies' ineligibility (see acknowledgments).

Eligibility Assessment and Data Extraction

Two authors (CNS and AM) independently screened titles and abstracts of retrieved records, with full-text reviews conducted to confirm eligibility based on the inclusion and exclusion criteria. Discrepancies were resolved through discussion. Data extraction was performed using a pre-tested Microsoft Excel form, with features like drop-down menus to reduce errors. All key data points were rechecked for accuracy, and sensitivity analyses were conducted to evaluate the impact of methodological decisions (e.g., imputing zeros in placebo arms when adverse events were only reported for the AZM group).

Collected data included participant demographics (e.g., age, gender, BMI), intervention details (e.g., AZM dose, treatment duration, renal function adjustments (19)), relevant lab results (e.g., pH (16), bicarbonate (19), chloride levels (20)), and side effect occurrences (primary outcomes: paraesthesia, dysgeusia, polyuria, fatigue). For each side effect, we documented the number of participants experiencing it in the AZM and placebo groups, while lab data focused on mean values post-treatment administration.

Statistical Analysis

Data Preparation: For placebo arms that served as comparators for multiple AZM doses, participant data were evenly divided to prevent unit-of-analysis errors while enabling dose-dependent effect assessments (11, 25). Studies with no reported events in either group were included in the primary analysis using a continuity correction of 0.5 for all cells, assuming side effect frequency might vary with AZM dose. Excluding these studies could disproportionately eliminate low-dose trials, inflating risk estimates for lower doses and reducing power to detect dose dependency (26).

Side Effect Risk: For side effects reported by three or more studies, pooled effect estimates were calculated using the Mantel-Haenszel method with a fixed-effects model to minimize small-study bias. Odds ratios (ORs) were used for their statistical advantages, but final results were converted into risk ratios (RRs) and numbers needed to treat (NNT) for clearer interpretation (25, 27). Heterogeneity was assessed using the I^2 statistic and categorized as low (<30%), moderate (30%–50%), or high (>50%) (25, 28). Random-effects models were used if heterogeneity remained >30%

Results

Included Studies

A total of 53 studies were identified that discussed one or more side effects (6, 15, 29–77). Seven additional references were located through the examination of reference lists (5, 6, 7, 68, 78–80 from one source; 12, 18 from another; and 82 and 13 from another). Among these, only two studies (6, 7, 68) met the criteria for inclusion in this review. Two publications (6, 42) provided data from two different treatment groups comparing varying AZM dosages to placebo, resulting in each article contributing two studies to the analysis, 35 study were included at the end

Approximately one-third of the trial participants were women, with average ages ranging widely from 19 to 74 years, and body mass index (BMI) values spanning from 20 to 40 kg/m². studies reported race distribution, with 79% of participants identified as White, 16% as Black, and 5%

from other racial groups. Nearly half of the studies evaluated AZM's effects on acute or chronic mountain sickness (48%), while other conditions included intraocular pressure (17%) and sleep-disordered breathing (10%). The remaining studies examined a variety of conditions.

Around 50% of the trials actively investigated side effects, with risk of overall bias rated as low in 24% and unclear in 33% of studies. On average, 30 participants were included per AZM treatment group, receiving a mean dosage of 542 mg/day (ranging from 125 to 4000 mg) over an average duration of 17 days (range: 1–180 days). Renal function considerations were reported in one-third of studies, and 7% of trials included potassium supplementation.

AZM use was associated with increased odds for the primary side effects: paraesthesias dysgeusia, polyuria, and fatigue . The odds ratios (ORs) ranged from 1.9 to 12.3, with evidence quality ranging from low to moderate. For paraesthesias, dysgeusia, and fatigue, meta-regression analysis revealed a 2-3 fold increase in odds with each incremental increase in daily AZM dose (400 mg vs. 400–600 mg vs. >600 mg). However, the confidence interval (CI) for fatigue included no increase in risk at higher doses. No dose-dependent relationship was found for polyuria .

Further subgroup analyses demonstrated a 1.5–4 fold higher risk of side effects when symptoms were actively monitored compared to passive monitoring, although the CI for dysgeusia alone excluded the null. For fatigue, a 1.4-fold increase in odds was observed with every 10% rise in female participants, but the CI remained wide (0.9–2.1). Side effect risks for most outcomes slightly increased with longer AZM use or higher cumulative doses, but effect sizes were minor, and CIs often included the null . Overall, the risk of bias did not appear to influence these results significantly.

The number needed to treat for harm (NNTH)—representing the number of individuals needing treatment for one additional side effect to occur—ranged from 2.3 for paraesthesias to 18 for dysgeusia.

AZM was associated with a 2.6–4 fold increased risk of nausea, gastroesophageal reflux disease , diarrhea , and depression . Additionally, the drug increased the odds of drowsiness,tinnitus, dyspnea , and dry mouth by 2.3–4.7 times, though the lower CI occasionally included the null. Lesser increases in dizziness and rash were observed, but with wide CIs that included the null.

Rarely reported side effects included hypokalemia, noted in studies involving doses of 500–4000 mg/day, typically in combination with hydrochlorothiazide or valsartan .Additionally, metabolic acidosis was reported in studies involving severely ill hospitalized patients. Rare laboratory

changes included a single case each of severe transaminitis (29) and hematologic dyscrasia (29). Exercise tolerance appeared reduced in four studies (70, 72–74), but variations in assessment methods prevented meaningful data pooling.

Table 1. Characteristics of studies included into quantitative analyses (n=42)

Study characteristics	Mean (SD) or % ($N_{Studies}$)	Range
General		
Age, years	44 (15)	19 to 74
% female	36 (29)	0 to 98
BMI, kg/m^2	27 (5.6)	20 to 40
Weight, kg	75 (18)	51 to 108
Height, cm	165 (5.4)	160 to 174
Race		
White	79.2 (17)	63 to 100
Black	16 (13)	0 to 30
Other	5.2 (4.4)	0 to 11
Condition		
Acute/chronic mountain sickness	48 (20)	Na
Sleep disordered breathing	10 (4)	Na
Ophthalmologic condition (medical)	10 (4)	Na
Ophthalmologic surgery	7 (3)	Na
Other*	26 (11)	Na
Diuretic use		
Yes	12 (5)	Na
Unclear/no	88 (37)	Na
Query type (for side effects)		
Active	52 (22)	Na
Unclear/passive	48 (20)	Na
Overall bias†		
Low	24 (10)	Na
Unclear	33 (14)	Na
High	43 (18)	Na
Intervention		
Acetazolamide		
Total daily dose‡, mg	542 (371)	125 to 4000 §
Total daily dose/kg‡, mg/kg	6.9 (4.6)	3.1 to 23
Total daily dose (categorical)		
<400 mg	29 (12)	Na
400–600 mg	50 (21)	Na
>600 mg	21 (9)	Na
Doses per day	1.8 (0.7)	1 to 4
Days of administration (continuous)	17 (32)	1 to 180

Days of administration (categorical)		
<3 days	26 (11)	Na
3 to 7 days	40 (17)	Na
>7 days	33 (14)	Na
Cumulative dose¶, 1000*mg*days	17 (68.3)	0.125 to 450
Renal adjustment		
Yes**	31 (13)	Na
No	69 (29)	Na
K supplementation		
Standing	5 (2)	Na
As needed	2 (1)	Na
Unclear/no	93 (39)	Na
No. subjects, acetazolamide arm	30 (25)	6 to 118
No. subjects, placebo arm	29 (25)	5 to 119
	Mean difference	**range**
pH	−0.07 (0.02)	−0.11 to −0.02
pCO_2	−2.8 (2.8)	−6.7 to 2.9
pO_2	4.9 (3.4)	0.7 to 10.5
Bicarbonate	−4.5 (1.4)	−7 to −2.9
Chloride	3.3 (0.3)	3 to 3.6
Sodium	0 (1.4)	−1 to 2
Potassium	−0.3 (0.1)	−0.5 to −0.2
Creatinine	Na	Na

Discussion

The analysis confirms that adverse effects like paraesthesias, dysgeusia, and potentially fatigue are influenced by dosage levels. Severe side effects were found to be infrequent and generally limited to specific patient groups. For example, hypokalaemia was nearly exclusively observed in individuals concurrently taking thiazide diuretics or angiotensin-receptor blockers (29, 48), consistent with findings from studies not included in this review (14, 16). Similarly, metabolic acidosis was noted primarily in hospitalized patients with severe illnesses (35, 47), dyspnoea occurred in patients with pre-existing respiratory strain (43), and fatalities were reported in critically ill patients, such as those with HIV/cryptococcal meningitis. Additionally, one case of severe liver enzyme elevation (transaminitis) was identified without clear contributing factors (29). This review is valuable for several reasons. First, clinical decisions hinge on balancing risks and benefits, yet much of the existing literature emphasizes benefits, potentially biasing judgments in favor of interventions (84, 85). Our findings complement a previous BMJ review assessing AZM's effectiveness in preventing acute mountain sickness (AMS) (11), enabling a more balanced

evaluation of the drug's overall utility across various conditions. Second, the results offer practical guidance for clinicians, suggesting that initiating treatment with low doses of AZM may minimize some side effects and that dose reductions may help manage these effects if they occur. Third, our findings reinforce prior efforts to determine the minimal effective dose of AZM for AMS prevention (11, 42, 86) and underline the need to establish appropriate dosing for other medical uses.

Some side effects, particularly subjective ones, are susceptible to placebo effects, as evidenced by high event rates in placebo groups. To address this, our review focused solely on placebo-controlled trials, but our pooled estimates for common side effects align well with observational data (2, 16). However, the analysis did not confirm the influence of factors like renal function (19, 21), weight (21), race (2), or laboratory changes (16, 20), likely due to insufficient data, limited power for meta-regression in small study samples, and potential confounding in observational analyses. The observed dose dependence for paraesthesias, dysgeusia, and fatigue is supported by several findings: randomized trials comparing 250 mg to 500–750 mg doses reported higher rates of paraesthesias and dysgeusia in the higher dose groups (6, 42), and AZM's pharmacodynamic effects vary with dose levels (18). For instance, lower doses (125–350 mg) primarily affect renal carbonic anhydrase (CA), inducing metabolic acidosis and promoting steady-state ventilation, which is crucial for AMS prevention (18, 88). At higher doses (500–1400 mg), AZM increasingly inhibits intracellular CA, potentially exacerbating side effects like fatigue (18, 20).

Some gastrointestinal side effects appear independent of dose and may stem from local irritation, which may improve when AZM is taken with food (16). Our findings align with prior systematic reviews that assessed a limited range of side effects (11, 12) and observational studies reporting similar risks for paraesthesias (10). Nonetheless, our study has limitations. Restricting the database search to two sources may have excluded relevant studies. However, the use of widely adopted databases and extensive reference reviews minimized this risk.

The study's strengths include large sample sizes, a broad evaluation of side effects, and rigorous sensitivity analyses. Limitations include the potential variability of side effects over time (63, 90), lack of detailed time-to-event data, and limited analysis of how side effects influence therapy adherence. Notably, adherence decisions likely involve multiple factors, including side effect type, severity, and psychosocial elements like partner support (91). Additionally, our findings may not generalize to hospitalized or severely ill populations, as most data came from relatively healthy

outpatients. Certain rare side effects, such as nephrolithiasis or AZM-induced hypoxaemia, may have been underrepresented due to shorter trial durations.

Although focused on AZM, these findings may extend to other CA inhibitors like methazolamide or topiramate, which exhibit distinct pharmacological profiles and tolerability (93, 95). The complexity of CA inhibition, involving multiple isoforms, underscores the need for further research to understand drug-specific differences and optimize clinical use (18, 93).

Conclusion

Paraesthesias are the most frequently reported side effect of AZM, potentially impacting compliance. However, they may be less likely to lead to therapy discontinuation compared to fatigue and gastrointestinal symptoms. Lower doses of AZM can reduce the likelihood of paraesthesias, dysgeusia, and fatigue, while gastrointestinal symptoms may improve with food. Severe adverse effects are uncommon and largely preventable through careful patient selection, such as avoiding concurrent use of thiazide diuretics to mitigate hypokalaemia. By complementing efficacy data, these findings support balanced clinical decision-making and emphasize the need to tailor AZM dosing based on condition-specific requirements.

References

1.Leaf A, Schwartz WB, Relman AS. Oral administration of a potent carbonic anhydrase inhibitor (diamox). I. changes in electrolyte and acid-base balance. N Engl J Med 1954;250:759–64. 10.1056/NEJM195405062501803

2.Becker B, Middleton WH. Long-Term acetazoleamide (diamox) administration in therapy of glaucomas. AMA Arch Ophthalmol 1955;54:187–92. 10.1001/archopht.1955.00930020191004

3.Forwand SA, Landowne M, Follansbee JN, et al. . Effect of acetazolamide on acute mountain sickness. N Engl J Med 1968;279:839–45. 10.1056/NEJM196810172791601

4.White DP, Zwillich CW, Pickett CK, et al. . Central sleep apnea. improvement with acetazolamide therapy. Arch Intern Med 1982;142:1816–9.

5.Wagenaar M, Vos P, Heijdra Y, et al. . Comparison of acetazolamide and medroxyprogesterone as respiratory stimulants in hypercapnic patients with COPD. Chest 2003;123:1450–9. 10.1378/chest.123.5.1450

6.Richalet J-P, Rivera M, Bouchet P, et al. . Acetazolamide: a treatment for chronic mountain sickness. Am J Respir Crit Care Med 2005;172:1427–33. 10.1164/rccm.200505-807OC

7., Wall M, McDermott MP, et al. , NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee . Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. JAMA 2014;311:1641–51. 10.1001/jama.2014.3312

8.Mincione F, Scozzafava A, Supuran CT. The development of topically acting carbonic anhydrase inhibitors as anti-glaucoma agents. Curr Top Med Chem 2007;7:849–54. 10.2174/156802607780636735

9.Berson FG, Epstein DL, Grant WM, et al. . Acetazolamide dosage forms in the treatment of glaucoma. Arch Ophthal 1980;98:1051–4. 10.1001/archopht.1980.01020031041005

10.Nieto Estrada VH, Molano Franco D, Medina RD, et al. . Interventions for preventing high altitude illness: Part 1. Commonly-used classes of drugs. Cochrane Database Syst Rev 2017;6:Cd009761. 10.1002/14651858.CD009761.pub2

11.Low EV, Avery AJ, Gupta V, et al. . Identifying the lowest effective dose of acetazolamide for the prophylaxis of acute mountain sickness: systematic review and meta-analysis. BMJ 2012;345:e6779 10.1136/bmj.e6779

12.Kayser B, Dumont L, Lysakowski C, et al. . Reappraisal of acetazolamide for the prevention of acute mountain sickness: a systematic review and meta-analysis. High Alt Med Biol 2012;13:82–92. 10.1089/ham.2011.1084

13.Simancas-Racines D, Arevalo-Rodriguez I, Osorio D, et al. . Interventions for treating acute high altitude illness. Cochrane Database Syst Rev 2018;6:Cd009567. 10.1002/14651858.CD009567.pub2

14.Edwards BA, Sands SA, Eckert DJ, et al. . Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. J Physiol 2012;590:1199–211. 10.1113/jphysiol.2011.223925

15.Basnyat B, Gertsch JH, Johnson EW, et al. . Efficacy of low-dose acetazolamide (125 Mg Bid) for the prophylaxis of acute mountain sickness: a prospective, double-blind, randomized, placebo-controlled trial. High Alt Med Biol 2003;4:45–52. 10.1089/152702903321488979

16.Epstein DL, Grant WM. Carbonic anhydrase inhibitor side effects. Arch Ophthal 1977;95:1378–82. 10.1001/archopht.1977.04450080088009

17.Alper AB, Tomlin H, Sadhwani U, et al. . Effects of the selective cyclooxygenase-2 inhibitor analgesic celecoxib on renal carbonic anhydrase enzyme activity: a randomized, controlled trial. Am J Ther 2006;13:229–35. 10.1097/01.mjt.0000182359.63457.01

18.Swenson ER. Carbonic anhydrase inhibitors and ventilation: a complex interplay of stimulation and suppression. Eur Respir J 1998;12:1242–7. 10.1183/09031936.98.12061242

19.Chapron DJ, Gomolin IH, Sweeney KR. Acetazolamide blood concentrations are excessive in the elderly: propensity for acidosis and relationship to renal function. J Clin Pharmacol 1989;29:348–53. 10.1002/j.1552-4604.1989.tb03340.x

20.Inatani M, Yano I, Tanihara H, et al. . Relationship between acetazolamide blood concentration and its side effects in glaucomatous patients. J Ocul Pharmacol Ther 1999;15:97–105. 10.1089/jop.1999.15.97

21.Yano I, Takayama A, Takano M, et al. . Pharmacokinetics and pharmacodynamics of acetazolamide in patients with transient intraocular pressure elevation. Eur J Clin Pharmacol 1998;54:63–8. 10.1007/s002280050422

22.Moher D, Liberati A, Tetzlaff J, et al. . Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535. 10.1136/bmj.b2535

23.Cui JH, Wang YH, Zhan XZ, et al. . Acetozolamide and highland-vitamin-tablet for improving the recovery after exhaustion exercise at high altitude. Chinese Journal of Clinical Rehabilitation 2004;8:5100–2.

24.Sajedi P, Soleimani P. Investigating the effect of two doses of acetazolamide, as a precursor for relief of referral pain, after laparoscopic cholecystectomy with carbon dioxide gas, and comparing it with control group. Journal of Isfahan Medical School 2018;36:621–8.

25.Higgins JPT, Green S. Cochrane Handbook for systematic reviews of interventions version 5.1.0, 2019. www.handbook.cochrane.org

26.Friedrich JO, Adhikari NKJ, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. BMC Med Res Methodol 2007;7:5 10.1186/1471-2288-7-5

27.Altman DG. Confidence intervals for the number needed to treat. BMJ 1998;317:1309–12. 10.1136/bmj.317.7168.1309

28.Higgins JPT, Thompson SG, Deeks JJ, et al. . Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60. 10.1136/bmj.327.7414.557

29.ten Hove MW, Friedman DI, Patel AD, et al. . Safety and tolerability of acetazolamide in the idiopathic intracranial hypertension treatment trial. J Neuroophthalmol 2016;36:13–19. 10.1097/WNO.0000000000000322

30.Sharma S, Gralla J, Ordonez JG, et al. . Acetazolamide and N-acetylcysteine in the treatment of chronic mountain sickness (Monge's disease). Respir Physiol Neurobiol 2017;246:1–8. 10.1016/j.resp.2017.07.005

31.Hamidi M, Aghamir SMK, Salavati A, et al. . A pilot randomized study on use of oral acetazolamide in patients with refractory dysuria. Int Urol Nephrol 2017;49:927–30. 10.1007/s11255-017-1566-2

32.Bala I, Bhatia N, Mishra P, et al. . Comparison of preoperative oral acetazolamide and intraperitoneal normal saline irrigation for reduction of postoperative pain after laparoscopic cholecystectomy. J Laparoendosc Adv Surg Tech A 2015;25:285–90. 10.1089/lap.2014.0507

33.Ulrich S, Keusch S, Hildenbrand FF, et al. . Effect of nocturnal oxygen and acetazolamide on exercise performance in patients with pre-capillary pulmonary hypertension and sleep-disturbed breathing: randomized, double-blind, cross-over trial. Eur Heart J 2015;36:615–23. 10.1093/eurheartj/eht540

34.Ke T, Wang J, Swenson ER, et al. . Effect of acetazolamide and gingko biloba on the human pulmonary vascular response to an acute altitude ascent. High Alt Med Biol 2013;14:162–7. 10.1089/ham.2012.1099

35.Gulsvik R, Skjørten I, Undhjem K, et al. . Acetazolamide improves oxygenation in patients with respiratory failure and metabolic alkalosis. Clin Respir J 2013;7:390–6. 10.1111/crj.12025

36.Wang J, Ke T, Zhang X, et al. . Effects of acetazolamide on cognitive performance during high-altitude exposure. Neurotoxicol Teratol 2013;35:28–33. 10.1016/j.ntt.2012.12.003

37.Latshang TD, Nussbaumer-Ochsner Y, Henn RM, et al. . Effect of acetazolamide and AutoCPAP therapy on breathing disturbances among patients with obstructive sleep apnea syndrome who travel to altitude. JAMA 2012;308:2390–8. 10.1001/jama.2012.94847

38.Nussbaumer-Ochsner Y, Latshang TD, Ulrich S, et al. . Patients with obstructive sleep apnea syndrome benefit from acetazolamide during an altitude sojourn: a randomized, placebo-controlled, double-blind trial. Chest 2012;141:131–8. 10.1378/chest.11-0375

39.van Patot MCT, Leadbetter G, Keyes LE, et al. . Prophylactic low-dose acetazolamide reduces the incidence and severity of acute mountain sickness. High Alt Med Biol 2008;9:289–93. 10.1089/ham.2008.1029

40.Richalet J-P, Rivera-Ch M, Maignan M, et al. . Acetazolamide for Monge's disease: efficiency and tolerance of 6-month treatment. Am J Respir Crit Care Med 2008;177:1370–6. 10.1164/rccm.200802-196OC

41.Hillenbrand P, Pahari AK, Soon Y, et al. . Prevention of acute mountain sickness by acetazolamide in Nepali porters: a double-blind controlled trial. Wilderness Environ Med 2006;17:87–93. 10.1580/1080-6032-17.2.87

42.Basnyat B, Gertsch JH, Holck PS, et al. . Acetazolamide 125 Mg BD is not significantly different from 375 Mg BD in the prevention of acute mountain sickness: the prophylactic acetazolamide dosage comparison for efficacy (PACE) trial. High Alt Med Biol 2006;7:17–27. 10.1089/ham.2006.7.17

43.Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. Am J Respir Crit Care Med 2006;173:234–7. 10.1164/rccm.200507-1035OC

44.Chow T, Browne V, Heileson HL, et al. . Ginkgo biloba and acetazolamide prophylaxis for acute mountain sickness: a randomized, placebo-controlled trial. Arch Intern Med 2005;165:296–301. 10.1001/archinte.165.3.296

45.Gertsch JH, Basnyat B, Johnson EW, et al. . Randomised, double blind, placebo controlled comparison of Ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the prevention of high altitude illness trial (PHAIT). BMJ 2004;328:797 10.1136/bmj.38043.501690.7C

46.Fischer R, Lang SM, Leitl M, et al. . Theophylline and acetazolamide reduce sleep-disordered breathing at high altitude. Eur Respir J 2004;23:47–52. 10.1183/09031936.03.00113102

47.Newton PN, Thai LH, Tip NQ, et al. . A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. Clin Infect Dis 2002;35:769–72. 10.1086/342299

48.Vahedi K, Taupin P, Djomby R, et al. . Efficacy and tolerability of acetazolamide in migraine prophylaxis: a randomised placebo-controlled trial. J Neurol 2002;249:206–11. 10.1007/PL00007866

49.Gunal DI, Afşar N, Bekiroglu N, et al. . New alternative agents in essential tremor therapy: double-blind placebo-controlled study of alprazolam and acetazolamide. Neurol Sci 2000;21:315–7. 10.1007/s100720070069

50.Moldow B, Sander B, Larsen M, et al. . The effect of acetazolamide on passive and active transport of fluorescein across the Blood-Retina barrier in retinitis pigmentosa complicated by macular oedema. Graefes Arch Clin Exp Ophthalmol 1998;236:881–9. 10.1007/s004170050175

51.Ladas ID, et al. Topical 2.0% dorzolamide vs oral acetazolamide for prevention of intraocular pressure rise after neodymium:YAG laser posterior capsulotomy. Arch Ophthal 1997;115:1241–4. 10.1001/archopht.1997.01100160411003

52.Whitcup SM, Csaky KG, Podgor MJ, et al. . A randomized, masked, cross-over trial of acetazolamide for cystoid macular edema in patients with uveitis. Ophthalmology 1996;103:1054–63. 10.1016/S0161-6420(96)30567-8

53.Vos PJ, Folgering HT, de Boo TM, et al. . Effects of chlormadinone acetate, acetazolamide and oxygen on awake and asleep gas exchange in patients with chronic obstructive pulmonary disease (COPD). Eur Respir J 1994;7:850–5.

54.Farber MD, Lam S, Tessler HH, et al. . Reduction of macular oedema by acetazolamide in patients with chronic iridocyclitis: a randomised prospective crossover study. Br J Ophthalmol 1994;78:4–7. 10.1136/bjo.78.1.4

55.Ladas ID, Pavlopoulos GP, Kokolakis SN, et al. . Prophylactic use of acetazolamide to prevent intraocular pressure elevation following Nd-YAG laser posterior capsulotomy. Br J Ophthalmol 1993;77:136–8. 10.1136/bjo.77.3.136

56.Grissom CK, et al. Acetazolamide in the treatment of acute mountain sickness: clinical efficacy and effect on gas exchange. Ann Intern Med 1992;116:461–5. 10.7326/0003-4819-116-6-461

57.Fishman GA, et al. Acetazolamide for treatment of chronic macular edema in retinitis pigmentosa. Arch Ophthal 1989;107:1445–52. 10.1001/archopht.1989.01070020519031

58.Metcalfe TW, Etchells DE. Prevention of the immediate intraocular pressure rise following argon laser trabeculoplasty. Br J Ophthalmol 1989;73:612–6. 10.1136/bjo.73.8.612

59.Whyte KF, Gould GA, Airlie GA, et al. . Role of protriptyline and acetazolamide in the sleep apnea/hypopnea syndrome. Sleep 1988;11:463–72. 10.1093/sleep/11.5.463

60.Häcki MA, Waldeck G, Brändli O. [Acetazolamide in hypercapnic chronic obstructive lung disease--a renaissance?]. Schweiz Med Wochenschr 1983;113:110–4.

61.Larson EB, Roach RC, Schoene RB, et al. . Acute mountain sickness and acetazolamide. clinical efficacy and effect on ventilation. JAMA 1982;248:328–32.

62.Greene MK, Kerr AM, McIntosh IB, et al. . Acetazolamide in prevention of acute mountain sickness: a double-blind controlled cross-over study. BMJ 1981;283:811–3. 10.1136/bmj.283.6295.811

63.BMRESMSSG Acetazolamide in control of acute mountain sickness. Lancet 1981;1:180–3.

64.Collier DJ, Wolff CB, Hedges A-M, et al. . Benzolamide improves oxygenation and reduces acute mountain sickness during a high-altitude TREK and has fewer side effects than acetazolamide at sea level. Pharmacol Res Perspect 2016;4:e00203–12. 10.1002/prp2.203

65.Reinhart WH, Goerre S, Bärtsch P. Acetazolamide reduces the erythropoietin response to hypoxia at high altitude in humans. J Wilderness Med 1994;5:312–7. 10.1580/0953-9859-5.3.312

66.Rosenbaek JB, Pedersen EB, Bech JN. The effect of sodium nitrite infusion on renal function, brachial and central blood pressure during enzyme inhibition by allopurinol, enalapril or acetazolamide in healthy subjects: a randomized, double-blinded, placebo-controlled, crossover study. BMC Nephrol 2018;19 10.1186/s12882-018-1035-x

67.Utz G, Schlierf G, Barth P, et al. . [Prevention of acute mountain sickness using acetazolamide]. Munch Med Wochenschr 1970;112:1122–4.

68.Zell SC, Goodman PH. Acetazolamide and dexamethasone in the prevention of acute mountain sickness. West J Med 1988;148:541–5.

69.Faull OK, Robertson J, Thomas O, et al. . The effect of acetazolamide on saccadic latency at 3459 meters. Wilderness Environ Med 2015;26:72–7. 10.1016/j.wem.2014.08.017

70.Bradwell AR, Myers SD, Beazley M, et al. . Exercise limitation of acetazolamide at altitude (3459 M). Wilderness Environ Med 2014;25:272–7. 10.1016/j.wem.2014.04.003

71.Lalande S, Snyder EM, Olson TP, et al. . The effects of sildenafil and acetazolamide on breathing efficiency and ventilatory control during hypoxic exercise. Eur J Appl Physiol 2009;106:509–15. 10.1007/s00421-009-1042-5

72.Faoro V, Huez S, Giltaire S, et al. . Effects of acetazolamide on aerobic exercise capacity and pulmonary hemodynamics at high altitudes. J Appl Physiol 2007;103:1161–5. 10.1152/japplphysiol.00180.2007

73.Fulco CS, Muza SR, Ditzler D, et al. . Effect of acetazolamide on leg endurance exercise at sea level and simulated altitude. Clin Sci 2006;110:683–92. 10.1042/CS20050233

74.Garske LA, Brown MG, Morrison SC. Acetazolamide reduces exercise capacity and increases leg fatigue under hypoxic conditions. J Appl Physiol 2003;94:991–6. 10.1152/japplphysiol.00746.2001

75.Brechue WF, Koceja DM, Stager JM. Acetazolamide reduces peripheral afferent transmission in humans. Muscle Nerve 1997;20:1541–8.

76.Leys MJJ, van Slycken S, Nork TM, et al. . Acetazolamide affects performance on the Nagel II anomaloscope. Graefes Arch Clin Exp Ophthalmol 1996;234:S193–7. 10.1007/BF02343071

77.Burtscher M, Likar R. Leukonychia following high altitude exposure. High Alt Med Biol 2002;3:93–4. 10.1089/152702902753639612

78.Bradwell AR, Delamere JP, Mackintosh JH. Acetazolamide in the mountains. The Lancet 1981;317:730 10.1016/S0140-6736(81)92013-4

79.Nicholson AN, Smith PA, Stone BM, et al. . Altitude insomnia: studies during an expedition to the Himalayas. Sleep 1988;11:354–61. 10.1093/sleep/11.4.354

80.Kronenberg RS, Cain SM. Effects of acetazolamide on physiologic and subjective responses of men to 14,000 feet. SAM-TR-67-81. Tech Rep SAM-TR 1967:1–10.

81.Sansone VA, Burge J, McDermott MP, et al. . Randomized, placebo-controlled trials of dichlorphenamide in periodic paralysis. Neurology 2016;86:1408–16. 10.1212/WNL.0000000000002416

82.Schneider-Gold C, Schoser B, Ellrichmann G, et al. . Guideline myotonic dystrophies, Non-Dystrophic myotonias and periodic paralyses. Aktuelle Neurologie 2018;45:167–77.

83.Hackett PH, Rennie D, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. Lancet 1976;2:1149–55. 10.1016/S0140-6736(76)91677-9

84.Wise J. Side effects are under-reported in peer reviewed journals. BMJ 2016;354:i5075. 10.1136/bmj.i5075

85.Zorzela L, Golder S, Liu Y, et al. . Quality of reporting in systematic reviews of adverse events: systematic review. BMJ 2013;348:f7668 10.1136/bmj.f7668

86.Carlsten C, Swenson ER, Ruoss S. A dose-response study of acetazolamide for acute mountain sickness prophylaxis in vacationing tourists at 12,000 feet (3630 M). High Alt Med Biol 2004;5:33–9. 10.1089/152702904322963672

87.da Costa BR, Jüni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. Eur Heart J 2014;35:3336–45. 10.1093/eurheartj/ehu424

88.Sakamoto T, Nakazawa Y, Hashizume Y, et al. . Effects of acetazolamide on the sleep apnea syndrome and its therapeutic mechanism. Psychiatry Clin Neurosci 1995;49:59–64. 10.1111/j.1440-1819.1995.tb01858.x

89.Javaheri S, Sands SA, Edwards BA. Acetazolamide attenuates Hunter-Cheyne-Stokes breathing but augments the hypercapnic ventilatory response in patients with heart failure. Ann Am Thorac Soc 2014;11:80–6. 10.1513/AnnalsATS.201306-201OC

90.Dahl H, Norskov K, Peitersen E, et al. . Zinc therapy of ACETAZOLAMIDE-INDUCED side-effects. Acta Ophthalmol 1984;62:739–45. 10.1111/j.1755-3768.1984.tb05801.x

91.Crawford MR, Espie CA, Bartlett DJ, et al. . Integrating psychology and medicine in CPAP adherence – new concepts? Sleep Med Rev 2014;18:123–39. 10.1016/j.smrv.2013.03.002

92.Sharp JT, Druz WS, D'Souza V, et al. . Effect of metabolic acidosis upon sleep apnea. Chest 1985;87:619–24. 10.1378/chest.87.5.619

93.Swenson ER. Safety of carbonic anhydrase inhibitors. Expert Opin Drug Saf 2014;13:459–72. 10.1517/14740338.2014.897328

94.Adamson R, Swenson ER. Acetazolamide use in severe chronic obstructive pulmonary disease. pros and cons. Ann Am Thorac Soc 2017;14:1086–93. 10.1513/AnnalsATS.201701-016FR

95.Hoffmanová I, Sánchez D. Metabolic acidosis and anaemia associated with dorzolamide in a patient with impaired renal function. Br J Clin Pharmacol 2018;84:796–9. 10.1111/bcp.13499

96.Teppema LJ, Swenson ER. The noncarbonic anhydrase inhibiting acetazolamide analog N-methylacetazolamide reduces the hypercapnic, but not hypoxic, ventilatory response. Physiol Rep 2015;3:e12484. 10.14814/phy2.12484

97.Lichter PR, Newman LP, Wheeler NC, et al. . Patient tolerance to carbonic anhydrase inhibitors. Am J Ophthalmol 1978;85:495–502. 10.1016/S0002-9394(14)75247-X

98.Lichter PR. Reducing side effects of carbonic anhydrase inhibitors. Ophthalmology 1981;88:266–9. 10.1016/S0161-6420(81)35040-4

99.Maren TH. The relation between enzyme inhibition and physiological response in the carbonic anhydrase system. J Pharmacol Exp Ther 1963;139:140–53.