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REVIEW

Acetazolamide for the Prevention of Acute Mountain Sickness—A Systematic Review and Meta-analysis

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See the Editorial by Buddha Basnyat, pp. 281–283 of this issue.

Background. Acetazolamide has been reported to be effective in the prevention of acute mountain sickness (AMS). Our aim was to conduct a systematic review of randomized, placebo-controlled trials of acetazolamide in the prevention of AMS.
Methods. Studies were identified by searching the MEDLINE, Embase, Cochrane Clinical Trials Register, and ClinicalTrials.gov databases. Primary end point was difference in incidence of AMS between acetazolamide and placebo groups.
Results. Acetazolamide prophylaxis was associated with a 48% relative-risk reduction compared to placebo. There was no evidence of an association between efficacy and dose of acetazolamide. Adverse effects were often not systematically reported but appeared to be common but generally mild. One study found that adverse effects of acetazolamide were dose related.
Conclusions. Acetazolamide is effective prophylaxis for the prevention of symptoms of AMS in those going to high altitude. A dose of 250 mg/day has similar efficacy to higher doses and may have a favorable side-effect profile.

Acute mountain sickness (AMS), characterized by headache, light-headedness, fatigue, nausea, and insomnia, occurs primarily at altitudes above 2,500 m in those poorly acclimatized to such conditions. If untreated, this symptom complex can progress to the life-threatening conditions of high altitude cerebral edema and high altitude pulmonary edema.[1] It has been suggested that the carbonic anhydrase inhibitor acetazolamide is effective in the prevention of AMS when begun prior to ascent to altitude. However, for clinicians prescribing for those ascending to altitude, there has been a lack of clarity regarding the usefulness of acetazolamide, when and for whom it should be recommended, and the optimum dose. While guidelines published by the Wilderness Medical Society recommend acetazolamide for travelers under some circumstances,[2] the Union Internationale des Associations d'Alpinisme does not make a similar suggestion.[3] The side effect profile of acetazolamide includes paraesthesia, urinary frequency, and dysgeusia (taste disorder). As such unpleasant symptoms could affect compliance with treatment, it is desirable to determine the lowest effective dose in order to potentially minimize the harmful effects of acetazolamide.

Two systematic reviews of acetazolamide in the prevention of altitude-related symptoms have been published. The first, published in 1994, included trials measuring a diverse range of outcomes not limited to classic symptoms of AMS.[4] This review found evidence of a benefit associated with acetazolamide but the heterogeneity in measured outcomes limits interpretation in a clinical context. The second systematic review was published in 2000 and had more restrictive inclusion criteria—including only studies reporting the incidence of AMS as an end point.[5] The authors concluded that 750 mg/d of acetazolamide was effective in the prophylaxis of AMS but that there was no evidence of benefit from 500 mg/d. However, this review was limited by the small number of patients in the pooled analysis which significantly limited its power.

Since Dumont and colleagues published their review in 2000, a significant number of controlled trials have been reported, including several trials investigating

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doses of acetazolamide less than 750 mg/d. We decided to review the available evidence including these recent clinical trials. Our review was limited to trials with AMS as an end point. Since assessment of AMS is subjective and potentially prone to bias, we decided to include only randomized, placebo-controlled, double-blind studies which clearly defined the diagnosis of AMS.

Methods

A protocol for this review is available on the journal website (See Appendix S1, Supporting Information). In conducting and reporting this review, we were guided by the principles of the PRISMA consensus statement (www.prisma-statement.org).

Search Strategy and Data Collection

Inclusion criteria are outlined in full in the protocol. Briefly, we aimed to include any randomized, double-blind, placebo-controlled trial comparing acetazolamide with placebo for the prevention of AMS. Placebo control, double blinding and a clear definition of AMS were considered essential because of the subjective nature of the symptoms of AMS and the potential for bias in uncontrolled or unblinded trials. Diagnostic criteria for AMS were considered to be a clear statement detailing which patients were considered to have AMS or the reporting of scores from a validated tool for which guidelines on interpreting the score to diagnose AMS are available (eg, the Lake Louise questionnaire discussed below).

A literature search was conducted using the MEDLINE, Embase, Cochrane Clinical Trials Register, and ClinicalTrials.gov databases. Searches were conducted using the key words "acetazolamide" or "Diamox" in combination with "altitude," "acute mountain sickness," or "high altitude headache." Abstracts were then screened and the full text of any that were considered to possibly meet the inclusion criteria was obtained. Other systematic reviews and clinical practice guidelines were also screened for publications that might be appropriate for inclusion and any other studies referenced in publications reviewed were also considered. Language was not considered an exclusion criteria but only trials published in full were considered for inclusion.

Data were extracted from the published results by two researchers working independently (N. D. R. and A. V. B.). Data were collected and compared for consistency. Any discrepancies were resolved by mutual agreement, but if agreement could not be reached then the third researcher (W. T. A. T.) was given a casting vote. Inclusion or exclusion of studies was performed by mutual agreement once data were extracted. Bias within studies was assessed using the tool developed by the Cochrane Collaboration.[6]

Analysis

Our primary analysis was to compare the incidence of AMS with that of placebo. Prespecified secondary analyses were the influence of dose, maximum altitude, and rate of ascent on treatment effect and the incidence of adverse effects. Non-pre-specified secondary analysis was conducted addressing the influence of placebo group risk of altitude sickness and study design on treatment effect.

Statistical analysis was undertaken using R for Mac OS X v 2.13.1 (The R Foundation, 2011) and the metafor library (Wolfgang Viechtbauer, 2010). Meta-analysis was conducted using a random effects model with treatment effect expressed as relative risk unless otherwise stated. In the assessment of study-wide covariates, a mixed-effects model was used with the covariate as a moderator. Heterogeneity was assessed using the Cochrane Q and I^2 statistics. Bias between studies was assessed using funnel plots and the Egger test. Weighted regression models were fitted using the preds() function of the metafor package. Number needed to treat (NNT) was reported conservatively by rounding up to the next whole number.

Results

Search Results and Data Collection

The primary search was conducted in March 2011. The outcome of the search strategy is summarized in Figure 1. Thirty-six studies were identified for full text review but the full text of one study could not be obtained.[7] Nineteen studies were excluded for the reasons outlined in Figure 1[8–26] leaving 17 studies for inclusion in the qualitative synthesis with a total of 1,765 participants taking either placebo or acetazolamide included in the end-point analysis.[27–43] The included studies are summarized in Table 1. Nine studies included groups taking other drugs for comparison (ginkgo balboa,[32,35,36] spironolactone,[27] ibuprofen,[29]

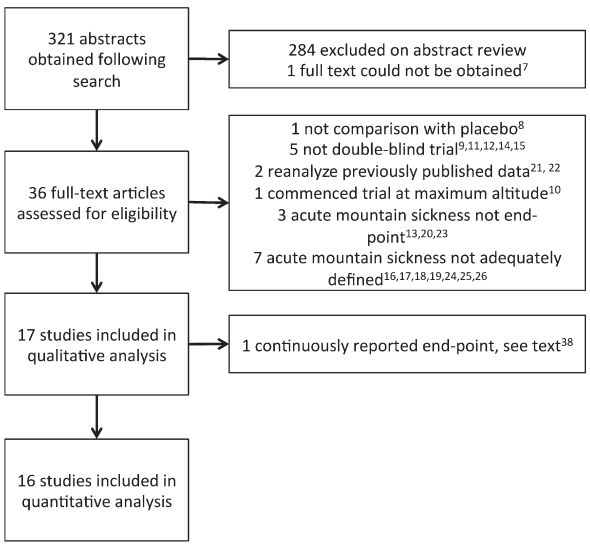

Figure 1 Summary of the results of literature search, review, and data extraction.

and dexamethasone[28,39–41]), but these other groups were not considered further in this analysis. Two studies presented outcome data on AMS in continuous form only[28,38] while the other 15 presented categorical data for AMS. In order to attempt to complete the categorical data, attempts were made to contact the corresponding authors of the two studies with continuous data. One author replied (A.W. Subudhi, personal communication, July 2011) with sufficient information to permit inclusion of the study in the pooled analysis of diagnosis of AMS.[28] No response was received from the other author and since this study contributed only 0.7% of study participants and would therefore have mimimal effect on the outcome of the analysis, these data were censored from quantitative analysis but included in the qualitative analysis.[38]

Study Design

Studies were included because they met the inclusion criteria and were therefore all randomized, double-blind, placebo-controlled trials comparing acetazolamide with placebo for the prevention of AMS. However, there was considerable heterogeneity in terms of study design.

Dose

Three different doses of acetazolamide were used (250, 500, and 750 mg/d; all in divided doses) and one study included a comparison between 250 and 750 mg/d as well as a placebo group.[33] For all analyses except where the impact of acetazolamide dose was being examined, the two active treatment groups in this trial were pooled into one group. One study used 255 mg/d and was included in the 250 mg/d group for purposes of analysis.[29] None of the trials report using modified release acetazolamide and divided daily dosing was used in all trials except one.[34]

Recruitment

We identified two different groups of clinical trials based on their recruitment method and found that this classification was useful in describing other important aspects of trial design and outcome. Eight of the clinical trials recruited trekkers as they ascended and then aimed to assess the same trekkers later on their expedition.[27,29,30,33,34,36,37,43] We designated this type of trial "location-based." The other nine trials, including the trial which was excluded from quantitative analysis, recruited people to the trial prior to embarking on an organized expedition(s) and we designated this type of trial "expedition-based."[28,31,32,35,38–42] There are a number of key differences between the two different types of trial summarized in Table 2. Most importantly, location-based trials tended to be larger (median 160.5 vs 35) but have a higher dropout rate (median 52 vs 0.5). Expedition-based trials had a higher rate of ascent (mean 450 vs 2,800 m/d).

End-point Assessment

All of the studies used questionnaires to assess outcome. These were either administered by blinded researchers or self-administered. A number of assessment tools were used as shown in Table 1. The most commonly used assessment score was the Lake Louise Symptom score (LLS),[44] which was used in 10 studies (63%). Four studies (25%) used variations of the Acute Mountain Sickness score cerebral and respiratory domains (AMS-C and AMS-R) which are derived from the modified Environmental Systems Questionnaire.[45] Of the remaining clinical trials, one used the General High Altitude Questionnaire (GHAQ)[46] and one used a score developed for the clinical trial.[43] All of the scores were similar in that they were combined interval scores incorporating several symptom domains and the diagnosis of AMS was made if a specific score was reached (often with the presence of headache mandatory). It is likely from the individual trial reports that timing of assessment after arrival at altitude varied; however, they generally did not contain enough information on this factor to allow analysis.

Within-study Bias

None of the study protocols were available for review. It was generally not possible to ascertain whether sequence generation, allocation, or blinding were satisfactory from the trial report since they were usually described briefly. However, no cause for concern about bias in any of these domains was found. All trials were therefore found to have low or unclear risk of bias in these domains. The main source of bias was found in the outcome data domain. As discussed above, studies which relied on location-based recruitment had a high dropout rate. We decided to perform a worst-case analysis of the missing data and exclude studies in which the worst-case analysis resulted in a change of result. Using this criteria, 7/8 location-based and 2/8 expedition-based studies were judged to have a high risk of bias. Because the study protocols were not available it was not possible to exclude selective reporting. However, one study recorded changing the primary analysis because the prespecified tool for the assessment of AMS was found not to be suitable and another was substituted.[41] This trial was therefore regarded as having a high risk of bias in this domain. Finally, one trial was found to have a potential risk of bias because subjects recruited into the trial were excluded unless they managed to ascend a further 800 m. Outcome data for subjects failing to ascend this further distance were not presented.

Of the 16 clinical trials, nine were therefore considered to have a high risk of bias while all the others had an unclear risk of bias in at least one domain.

Outcomes

Prevention of AMS

Sixteen studies were included in the primary analysis. Acetazolamide reduced the incidence of AMS in study

Table 1 Characteristics of included studies

First author	Year	Location	Study type*	Subjects	Number of subjects	Dose (mg)	Ascent range (m)	Approximate ascent rate (m/24 h)	Run in days	Duration (d)	Drop outs (%)	End point assessment
Basnyat[27]	2011	Himalayas	L	Trekkers	197	500	4,300–5,000	250	None	1–3	38 (19.3)	LLS ≥ 3 (with headache)
Subudhi[28]	2011	Simulated	E	Volunteers	49	750	0–4,875	4, 900	1	1	9 (31)	LLS ≥ 3
Gertsch[29]	2010	Himalayas	L	Trekkers	214	250	4,300–4,928	650	1.5	1–2	52 (24.3)	LLS ≥ 3 (with headache)
Basnyat[30]	2008	Himalayas	L	Trekkers	389	500	4,300–5,000	250	None	1–3	25 (6.4)	LLS ≥ 3 (with headache)
Tissot van Patot[31]	2008	Pikes Peak	E	Volunteers	44	250	2,000–4,300	2, 300	3	1	0 (0)	AMS-C ≥ 0.7 and LLS ≥ 3
Moraga[32]	2007	Andes	E	Volunteers	24	500	0–3,696	3, 700	1	1	0 (0)	LLS ≥ 3 (with headache)
Basnyat[33]	2006	Himalayas	L	Trekkers	197	250/750	3,440–4,928	350	None	<6	18 (9.1)	LLS ≥ 3 (with headache)
Hillenbrand[34]	2006	Himalayas	L	Nepali porters	400	250	3,440–4,930	300	None	<7	291 (72.8)	LLS ≥ 3 (with headache)
Chow[35]	2005	California	E	Volunteers	48	500	<500–3,800	2, 550	1	2	8 (17.8)	LLS ≥ 3 (with headache)
Gertsch[36]	2004	Himalayas	L	Trekkers	303	500	4,300–4,928	650	1.5	1–2	66 (21.8)	LLS ≥ 3 (with headache)
Basnyat[37]	2003	Himalayas	L	Trekkers	197	250	4,243–4,937	700	None	1–2	42 (21.3)	LLS ≥ 3 (with headache)
Hussain[38†]	2001	Pakistan	E	Volunteers	24	500	515–4,578	4, 050	1	5	0 (0)	ESQ ≥ 6
Ellsworth[39]	1991	Mount Ranier	E	Volunteers	16	250	1,300–4,392	1, 700	1	2	0 (0)	AMS-C or AMC-R
Zell[40]	1988	Nevada	E	Volunteers	15	500	2,100–3,650	900	2	2	0 (0)	AMS-C or AMS-R
Ellsworth[41]	1987	Mount Ranier	E	Volunteers	31	750	1,300–4,392	3, 050	1	2	1 (3.2)	AMS index ≥ 2
Larson[42]	1982	Mount Ranier	E	Volunteers	64	750	1,300–4,394	3, 150	1	2	5 (7.8)	GHAQ
Hackett[43]	1976	Himalayas	L	Trekkers	120§	500	3,440–>4,243	350	None	4‡	Approx 50%§	Symptom score ≥ 2

LLS = Lake Louise Symptom score; AMS-C = Acute Mountain Sickness score—Cerebral; AMS-R = Acute Mountain Sickness score—Respiratory; ESQ = modified Environmental Systems Questionnaire; GHAQ = Generalized High Altitude Questionnaire.

* For definition of study type see main text; E denotes expedition-based and L location-based.

† The study by Hussain and colleagues was excluded from the quantitative analysis (see main text).

‡ Acetazolamide was given for 4 days but the study was not complete until the participant returned to the study location.

§ Number of participants dropping out of the study could not be precisely calculated from the study text because included within that number was a control population not on study medication; 120 is the number of patients included in the final analysis.

Table 2 Summary of characteristics of studies with location-based and expedition-based recruitment

	Location	Expedition
Number of Studies	8	9
Location of studies	Approach to Mount Everest	Various geographic locations
Inclusion criteria	Healthy trekkers (7) Nepali porters (1)	Healthy volunteers (9)
Number of participants included in analysis, median (range)	160.5 (109–364)	35 (15–59)
Participants excluded from analysis, median (range)	52 (18–291)	0.5 (0–9)
Mean representative rate of ascent (m/d)*	450	2,800
Incidence of AMS in placebo group, mean % (SD)	26.9 (15.7)	48.9 (12.4)
Effect of acetazolamide on AMS, RR (95% CI)	0.51 (0.41–0.62)	0.52 (0.36–0.76)

AMS = acute mountain sickness.
* Rate of ascent rounded to nearest 50 m/d.

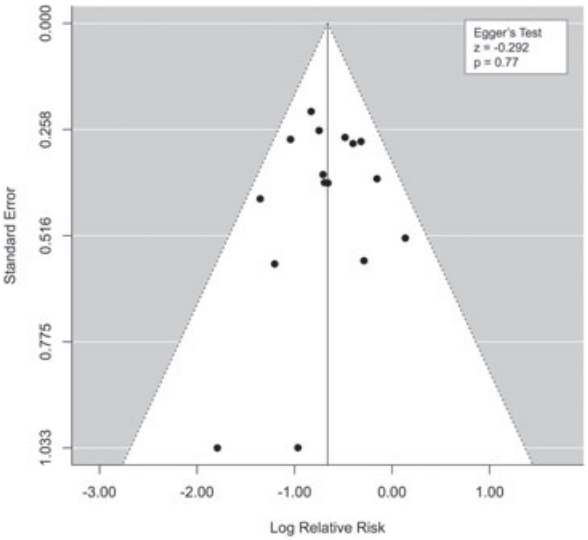

Figure 3 Funnel plot derived from primary analysis of acetazolamide versus placebo in all included clinical trials. An absence of symmetry could suggest bias by study size (ie, publication bias).

participants (Figure 2, RR 0.52, 95%CI 0.44-0.61, $p < 0.0001$). There was no evidence of significant heterogeneity ($p = 0.49$ by Cochrane's Q statistic, $I^2 = 0\%$). A funnel plot did not show evidence of asymmetry suggestive of underlying bias by study size ($p = 0.77$, Figure 3). There was also no evidence of any difference of treatment effect by trial design (pooled RR 0.51 vs 0.52, $p = 0.72$). We repeated the primary analysis

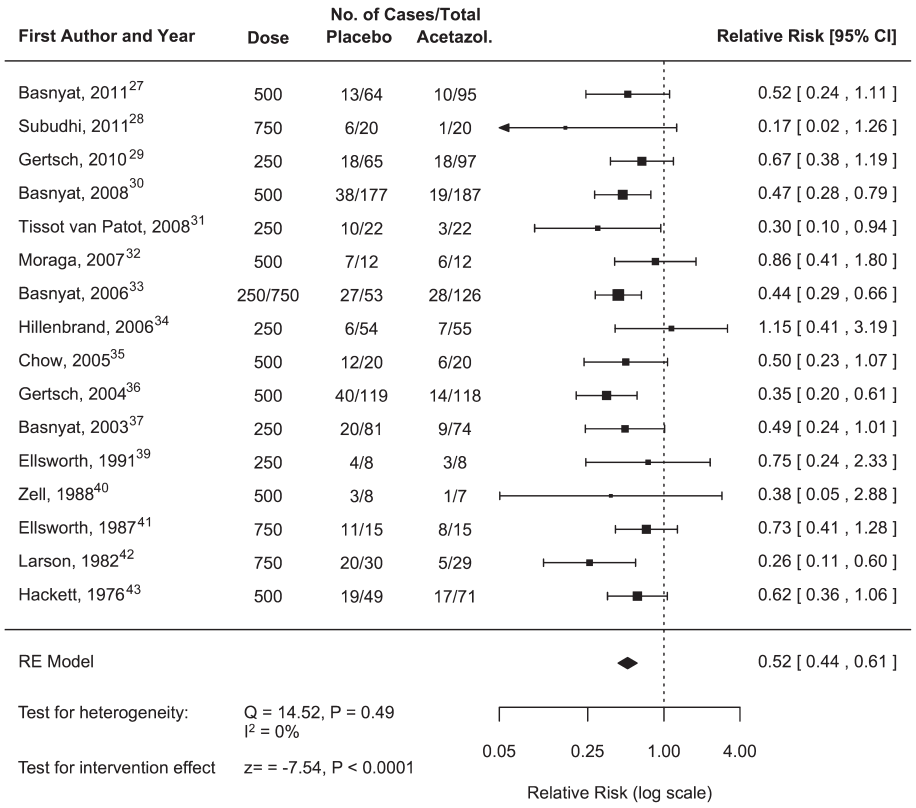

Figure 2 Forest plot depicting relative risk of acute mountain sickness in placebo and acetazolamide groups for all clinical trials. Dose is in mg/d. Relative risk <1 favors intervention.

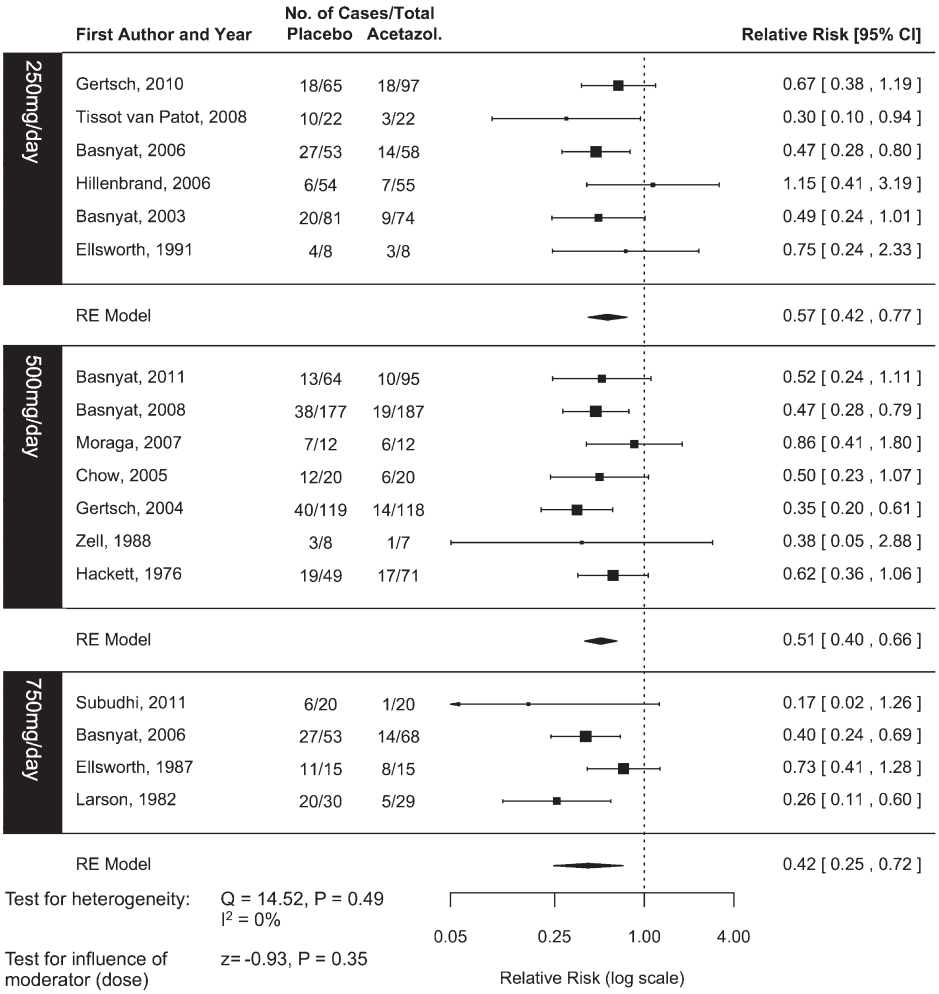

Figure 4 Influence of dose on treatment with acetazolamide. A pooled analysis for each dose was performed separately for each dose. Test for influence of dose used a mixed-effects model with dose as a moderator.

after excluding studies judged to have a high risk of bias as described above. The results of this analysis were similar to the primary analysis (RR 0.47, 95%CI 0.35–0.62, $p < 0.0001$). Since there was no significant difference in treatment effect or estimate of heterogeneity when this much more restrictive analysis was conducted, other analyses were conducted using all included clinical trials.

The analysis was repeated with acetazolamide dose as a moderator (Figure 4). There was no evidence of a difference in treatment effect with increasing doses of acetazolamide ($p = 0.35$). Since studies differed in the rate of AMS in the placebo group, we sought to explore the interaction between placebo risk and treatment benefit measured by absolute risk reduction. The incidence of AMS in the placebo group of each trial was plotted against the absolute risk reduction associated with acetazolamide in the trial. A weighted, meta-regression model was then used to assess the relationship. As could be implied by the consistent relative risk across the different trials, there was a strong, linear relationship between placebo risk and absolute risk reduction (Figure 5A). The model predicted a number needed to treat to prevent one case of AMS of 12 (95%CI 9–23) at a placebo risk of 20% while at a placebo risk of 40% the NNT fell to six (95%CI 5–7).

Maximum altitude reached was available for all but one study[43] and an approximate rate of ascent was calculated for each of the studies from the data available. Since rate of climb was not uniform, a representative rate of ascent was calculated based on data presented. This was particularly difficult to assess in location-based studies since participants climbed independently, therefore rates of climb are approximate. There was no evidence of an association between maximum height reached and absolute risk benefit (data not shown, $p = 0.36$). There was an association between rate of ascent and absolute risk benefit. The model was best fitted when the rate of ascent was log transformed (Figure 5B, $p = 0.005$).

One study included the prevention of high altitude pulmonary edema as a primary end point.[30] However, no cases of this condition occurred in the trial. Other

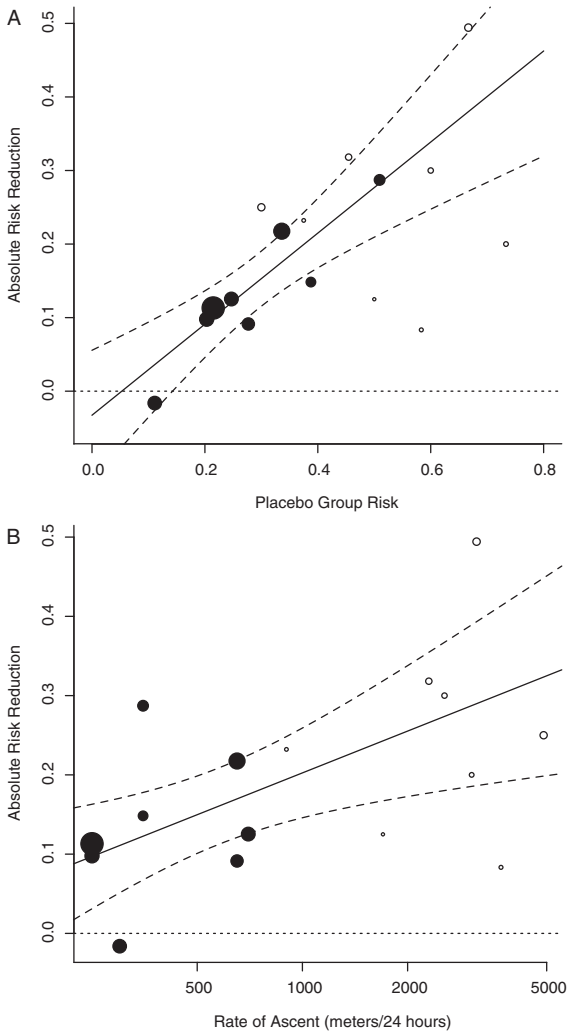

Figure 5 Association of (A) placebo group risk and (B) rate of ascent with absolute risk benefit. Solid circles denote location-based trials while open circles denote expedition-based trials. Solid lines represent the regression line with dashed lines representing 95% uncertainty boundaries. The size of each dot represents the weight associated with the trial. Note that rate of ascent is represented on a logarithmic axis.

studies did not systematically report the presence or absence of pulmonary or cerebral edema.

Adverse Effects

Most trials did not systematically report adverse effects. In those trials that did report adverse effects, they were reported commonly but were usually not severe. The most commonly reported adverse effects were paraesthesia, urinary frequency, and dysgeusia. On pooled analysis, paraesthesia and dysgeusia were more common in the acetazolamide group ($p < 0.0001$ and $p = 0.016$, respectively). However, in those trials that systematically reported adverse effects, discontinuation of study medication due to adverse effects was unusual. It was not possible to perform meta-analysis investigating the impact of dose on rate of adverse effects since the number of studies involving each dose was small with significant heterogeneity. One study reported a direct comparison between 250 and 750 mg/d.[33] It found that paraesthesia was more common in the 750 mg/d group with a trend toward increased incidence of dysgeusia.

Discussion

This systematic review synthesized data from randomized-controlled trials investigating the efficacy of acetazolamide prophylaxis in the prevention of altitude sickness. It found a significant benefit associated with acetazolamide treatment that was remarkably consistent across a range of heterogeneous trials. Overall, the meta-analysis suggested that taking acetazolamide prophylaxis is associated with a relative-risk reduction of around 48%. There was no evidence of any difference in efficacy between different doses of acetazolamide. This conclusion differs from that of Dumont and colleagues who concluded that while 750 mg/d was effective, lower doses were not.[5] This difference is likely due to three principal factors: most importantly, there have been a significant number of new trials published since 2000, many of which examined lower doses of acetazolamide. Furthermore, the inclusion criteria of our study were different as we included only double-blind studies. Finally, while our primary end point was relative-risk reduction, in Dumont and colleagues it was NNT, which may have made comparison between trials difficult given the heterogeneity in risk of AMS between trials. It is of note that the two different types of study included, expedition-based and location-based studies, did not differ in their estimate of treatment efficacy despite marked differences in the design of the two study types. This supports the idea that the evidence of treatment benefit may be generalizable beyond the populations included in these studies.

The absolute risk reduction associated with acetazolamide prophylaxis was associated with the risk of AMS in the trial placebo group and with the rate of ascent but not the maximum altitude reached. The lack of association with maximum altitude is not surprising, as rate of ascent was variable and in all but two studies the maximum height reached was between 4,000 and 5,000 m. This does not exclude the possibility of an association if a greater range of maximum altitudes had been studied. There was an association between a study's representative rate of ascent and absolute benefit from acetazolamide. This means that as rate of ascent increases, the NNT from acetazolamide prophylaxis decreases. This finding is plausible but should be interpreted with caution. The rate of ascent is only approximate and particularly in the location-based studies is difficult to define. Furthermore, since the expedition-based studies had a higher rate of climb than the location-based studies, these differences could be confounded by other differences in the trial design rather than rate of ascent. The association between rate

of climb and benefit from acetazolamide could only be definitively established by a properly controlled trial with randomized rates of ascent.

Adverse effects were not systematically described in the majority of studies and this made firm conclusions about the incidence of these adverse events difficult. Many studies reported only the lack of serious adverse events. It is clear, however, that adverse effects are common but generally mild. In the studies systematically reporting adverse effects, paraesthesia was most commonly reported. There were, however, insufficient data in this analysis to investigate any association between dose and adverse effects. This question was addressed in one of the studies, which concluded that adverse effects were more common in the 750 mg/d group.[33]

There are a number of limitations to our analysis. We decided to include in our analysis only studies involving acetazolamide. This study does not address the efficacy of other medications for the prophylaxis of AMS, such as dexamethasone, ibuprofen, and gingko balboa. A review on this broader question of the role of other pharmacological strategies has recently been published.[47] Since many of the early studies of acetazolamide in AMS were carried out many decades ago, it is likely that we have not identified all the studies which could have potentially been included. We were also unable to obtain the text of one study. However, given that this study and any possible unidentified studies are likely to be small, it is unlikely that they would have significantly altered this analysis. Our inclusion criteria were intentionally narrow, resulting in the exclusion of a significant number of trials. However, the requirement for a randomized, double-blind design, and a clear definition of what constituted a diagnosis of AMS reduce the risk of systematic bias. The studies used a variety of methods of end-point assessment, most commonly the LLS and AMS-C/AMS-R. While these scores do correlate, they have been observed to identify different populations of patients with AMS.[48,49] Furthermore, all the assessment tools for AMS suffer from having to apply an arbitrary cut-off to a complex clinical syndrome. These factors introduce a source of bias into our analysis; however, the lack of heterogeneity found in the assessment of the primary end point suggests that this effect is not large.

Our findings suggest that acetazolamide 250 mg/d is associated with a similar benefit compared to higher doses and that adverse effects are dose related. Therefore, a dose of acetazolamide 250 mg/d should be recommended in most instances based on current evidence. Future trials will clarify this understanding. Only one trial used a single daily dose of acetazolamide and this study, which was hampered by a low number of cases of AMS and a high dropout rate, failed to demonstrate a benefit of acetazolamide. Therefore, until further evidence emerges, divided daily dosing of acetazolamide should be suggested. This study could not address the interaction between dose and rate of ascent; further trials examining a range of doses in rapid ascent would be particularly helpful. In expedition-based trials, acetazolamide was started at low altitude whereas the location-based trials commenced treatment at moderate altitude. Both groups of trials demonstrated benefit from acetazolamide. However, since some patients in location-based studies were already experiencing altitude sickness when screened at moderate altitude, it would seem reasonable to commence acetazolamide at low elevations before ascending to a height where symptoms are likely. This analysis, however, provides limited evidence to assist prescribers in deciding which patients are likely to benefit most from acetazolamide treatment. Since studies with a high placebo risk and high ascent rate had a larger absolute risk benefit (Figure 5), this suggests that travelers judged to be at highest risk of AMS may benefit most from acetazolamide prophylaxis. The risk factors for AMS are well described and include not only altitude and rate of ascent but also personal factors such as history of AMS, young age, and a history of respiratory disease. Therefore, decisions on the prescribing of acetazolamide should be based on an individualized assessment of the risk of AMS weighed against the risk of adverse effects. This is the approach suggested by the Wilderness Medicine Society guidelines.[2]

Many tourists visiting East Africa join expeditions ascending Mount Kilimanjaro. On typical tourist expeditions rates of ascent are much higher than those recommended by published guidelines[50] and the incidence of AMS is high.[51,52] While advice to tourists intending to embark on these expeditions should include advice regarding the dangers of this rapid ascent, in our experience many travelers elect to proceed with their expedition as planned despite this warning. On the basis of our analysis, in such cases the use of prophylactic acetazolamide would appear to be justified. Only one of the studies in our analysis attempted to capture the incidence of high altitude pulmonary edema as a primary end point[30] and it failed to identify any cases during the trial, probably because subjects kept to modest rates of ascent. Our analysis is therefore unable to conclude anything about the efficacy of prophylactic acetazolamide in the prevention of the life-threatening complications of AMS. However, it is clear that many travelers continue to ascend even with symptoms of AMS.[53] It is important that whether acetazolamide is prescribed or not, travelers receive clear advice about what to do if symptoms develop. In the UK, acetazolamide is not licensed for the prevention of AMS, so patients should be specifically informed of this when prophylactic therapy is prescribed. As acetazolamide is a sulfa drug there is a theoretical concern in patients with a history of allergy to sulphonamide antibiotics; however, other experts argue that it can safely be given to patients with a history of such allergy.[54]

In conclusion, our systematic review has demonstrated strong evidence of a benefit of prophylactic acetazolamide in the prevention of AMS with a dose of 250 mg/d in divided doses offering similar efficacy to higher doses. Treatment is likely to be of greatest benefit to those at highest risk of developing AMS

but prophylactic prescribing is no substitute for good pre-travel advice regarding altitude-related symptoms.

Declaration of Interests

The authors state they have no conflicts of interest to declare.

Supporting Information

Supporting Information may be found in the online version of this article:

Appendix S1. Study protocol.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

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