e-Table 1. Limitations of prior literature cited in the introduction.

Study	Design and Side Effects	Comment/Limitations
Becker 1955[1]	Case series reporting efficacy and side effects of acetazolamide (mean total daily dose 1000mg) in 70 glaucoma patients treated for more than 6 months; the study reported the incidence of observed side effects including the following: - 61% paresthesias - 49% GI disturbance - 16% Excessive Fatigue - 4% "Urinary"	- High risk of bias[a] - Selection: high (only subjects who "adequately responded to initial acetazolamide therapy were included") - Performance: high (subjects were unblinded) - Detection: high (assessor were unblinded) - Attrition: unclear (unclear how subjects were selected, i.e. unclear how many subjects may not have followed up with physicians and thus not been included In this series) - Reporting: unclear (unclear how selected side effects, but report seems comprehensive) - Other: high (no control group) - No information about dose-dependence
Edwards 2012[2]	Randomized cross-over study of 12 OSA patients undergoing in random order a baseline sleep study without intervention and an overnight sleep study after 1 week of acetazolamide (1000mg/day). Reported side effects included: - 100% paresthesias - 25% nocturia - 8% hypokalemia	- High risk of bias[a] - Selection: unclear (subjects randomized, but randomization mechanism not described) - Performance: high (subjects were unblinded) - Detection: high (assessors were unblinded) - Attrition: low (all enrolled subjects accounted for)

		- Reporting: low (all planned outcomes were reported including side effects) - Other: low (no other concerns) - Low precision due to small sample size - No information about dose-dependence
Basnyat 2003[3]	Randomized placebo-controlled trial of 197 healthy trekkers being treated with acetazolamide 250mg/day vs placebo for prevention of acute mountain sickness; incidence of paresthesias was 49% vs 4% in the treatment vs control group; subjects with paresthesias were more likely to miss acetazolamide doses than those without paresthesias (21% vs 8%).	- Unclear risk of bias[a] -Selection: low (effectively randomized) - Performance: low (placebo) - Detection: low (placebo) - Attrition: unclear (21% attrition, but equal % across study groups) - Reporting: low - Other: low (no other concerns) - No information about dose-dependence
Alper 2006[4]	Randomized cross-over trial in which 10 subjects received celecoxib, acetazolamide (250-500mg/day) or placebo each for one week in a randomized order; primary outcomes were changes in lab results (bicarb, pH, chloride, etc); side effects were not reported	- No data on side effects
Swenson 1998[5]	Review article describing pharmacodynamic effects of acetazolamide at different doses	-No (original) data on side effects
Chapron 1989	Case series of 12 elderly patients treated with acetazolamide (mean 10mg/kg/day) for glaucoma (n=10) or pulmonary disease (n=2). Primary outcome was drug plasma levels and how they relate to renal function. This study showed that reduced renal function correlated with higher plasma levels and more pronounced acidosis. No side effects reported.	- No data on side effects
Yano 1998[6]	Case series of 17 patients with transient intra-occular pressure (IOP) elevations (in the setting of ophthalmic surgery) treated with acetazolamide (62.5 – 1000mg/day). Primary goal was to model pharmacokinetic an -dynamic	- No data on side effects

	effects. This study showed that plasma levels are correlated with renal function and that plasma levels of 4 mg/ml are needed to achieve 70% of Emax with regards to IOP. No side effects were reported.	
Low 2012[7]	Systematic review with main focus on identifying the lowest effective dose of acetazolamide to prevent acute mountain sickness. Incidence of side effects (paresthesias, polyuria, rash, dysgeusia) is provided from up to 5 original studies (without pooled effect estimates). Raw numbers mostly suggest higher incidence of side effects in studies using higher acetazolamide doses (250 vs 500 vs 750 mg).	- No pooled effects estimates, no confidence intervals or formal comparisons - Small sample size - Limited number side effects assessed
Kayser 2012[8]	Systematic review of acetazolamide's efficacy for preventing acute mountain sickness. Also reported pooled incidence of side effects (paresthesia, polyuria, dysgeusia) stratified by acetazolamide dose (250 vs 500 vs 750 mg). Risk ratios with confidence intervals excluding the null were considered statistically significant; based on this assessment the authors concluded "the risk of paresthesia was increased with all doses. The risk of polyuria and taste disturbance was increased with 500 and 750 mg". Dose dependence of side effects was not formally assessed.	- Limited number of studies (only studies using acetazolamide for preventing acute mountain sickness published prior to 2012) - Limited number side effects assessed - No formal assessment of dose-dependence

[a] For studies reporting side effects a risk of bias assessment was performed based on a modified version of the Cochrane's Risk of Bias tool. Note: 1.) This tool is primarily used for randomized studies but nonetheless provides a useful framework to identify potential risks of bias in studies in general (thus, to use a unified approach we used this tool rather than using the Newcastle Ottawa scale for the one non-randomized study); 2.) The standard tool has 5 domains, but for a more comprehensive assessment of non-randomized studies we added a 6th category "other"; 3.) We defined the overall risk of bias for each study as the "highest" level of bias across the 6 domains (high>unclear>low).

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