

**In Reply to Drs. Lipman and Hackett,**

**Word Count 941**

We appreciate the discourse from Drs. Lipman and Hackett<sup>1</sup>, value their insights, and welcome the opportunity to discuss our study<sup>2</sup>. Their main concern is that we have overestimated the expected incidence of AMS. We echo this concern and wish we could accurately know the true incidence of AMS at our study site. We attempted to estimate it as accurately as possible using available data. The studies they cited are not ideal for direct comparisons as they used different locations, elevations, ascent rates, methodologies, and inclusion / exclusion criteria than those in our study. Because of the site-specific variability of AMS incidence, it is important to compare only those studies that are nearly identical.

They state that there has been an “almost a 50% decline in AMS over the past 18 years, to 22% at the Himalayan Rescue Association clinic in Manang.” The studies conducted at 3519m in Manang, Nepal had a completely different trekking ascent profile and location. Our study was performed ~300 km away at ~1000m higher elevation, in Pheriche (4371m) and Dingboche (4410m), to Lobuche (4940m). Although we agree with their inference that lower incidence poses challenges to studying altitude illness in Manang, that was not our study site, nor was our methodology similar to that in the study they cited.

The SLEEP-AID study<sup>3</sup> cited did indeed originate in Pheriche and Dingboche. Unfortunately this study was also not comparable to ours due to the fact that AMS incidence was studied at different altitudes. The SLEEP-AID study was an overnight study while participants were staying in Pheriche and Dingboche. Our study and those we relied on for our power analysis

followed participants for at least 2 days as they ascended over 500m higher to Lobuje, where AMS incidence was then calculated. One would expect to find lower AMS incidence among subjects at a lower altitude for a shorter duration than in subjects trekking to a higher altitude followed over several days.

The authors argue that without a placebo arm one does not “know if these medications reduced the incidence of AMS at all.” We agree, but to identify or quantify the efficacy of these treatments relative to placebo was never the intent of our study. Rather our study purpose was to compare the efficacy of two treatments (ibuprofen and acetaminophen) relative to each other, in modifying AMS incidence. Questions examining the efficacy of these treatments relative to placebo have been addressed in numerous previous studies elsewhere. We did note that “combined group incidence of AMS was 19.1%, which is notably lower than the 33% averaged historical incidence,” and surmised that this apparent decrease in AMS incidence in both treatment groups relative to historical placebo levels likely resulted in part due to both treatments reducing AMS. This hypothesized explanation was based on prior studies showing ibuprofen’s efficacy at AMS prevention<sup>4</sup>. If indeed historical overall reductions of AMS incidence in trekkers at our study site are taking place, then that too could provide an additional explanation of at least some of the reduced AMS incidence we observed. That said, we examined whether ibuprofen and acetaminophen differed in the resulting incidence of AMS. We found little evidence to suggest that they do, concluding “acetaminophen performs similarly to ibuprofen in the prevention of AMS in partially acclimatized subjects.”

We concluded that there was not strong evidence of a difference. Our reported results specify the strength of that conclusion based on sample size. We calculated that the difference in AMS incidence between the two treatments was 7%, but concluded that in the population overall, the true difference might be anywhere between -4% and +16%. The uncertainty of our conclusion illustrates a limitation of sample size, but it does provide some likely bounds as to what differences are likely, should any exist, between the medications. Recruiting a third “placebo” arm to the study, would have required either fewer subjects in our treatment arms, or necessitated extending the trial over multiple trekking seasons. Possible declines in AMS incidence are far from conclusive. Larger sample sizes of Nepal trekkers (including multi-season recruitment) may be necessary for more precise estimates. Regardless, neither of these potential concerns invalidates our conclusions or indicates that it was an inappropriate approach to examine differences between ibuprofen and acetaminophen for prevention of AMS.

Lipman and Hackett’s estimation of our power calculations for our test of equivalency needs slight correction. We anticipated an incidence of about 14% AMS in our treatment groups, but wanted to be able to detect a difference between the two treatments as small as 11%, a difference that might be clinically relevant. For 80% power and  $\alpha=0.05$ , we estimated we would need at most 125 individuals in each arm. While we recruited more than that number of subjects, exclusions and a slightly higher than expected incidence of AMS resulted in a less precise estimate of the magnitude of difference between treatment arms.

Finally, we would also like to make a small correction; our manuscript stated an AMS incidence of 33% in our power calculation, not 32% as was cited. For the sake of openness and clarity it

has to be well-stated that we conducted our power analysis prior to conducting the study, based on multiple studies<sup>5,6,7,8</sup> with the same location, elevation, ascent profiles, recruitment methodologies, and time course. To calculate the historical AMS incidence we combined the results of these studies by dividing the number of subjects that developed AMS in the placebo arms by the total number of subjects in the placebo arms (omitting subjects that received interventions), we have  $44+16+40+20=120$  divided by  $109+53+119+81=362$ . The overall incidence of AMS in subjects taking placebo in these studies was  $120/362$  or 33%.

Respectfully,

Nicholas C. Kanaan, MD

Alicia L. Peterson, MD

Matiram Pun, MD

Peter S. Holck, PhD

Jennifer Starling, MD

Bikash Basyal, MD

Thomas F. Freeman, MD

Jessica R. Gehner, MD

- 92 Linda Keyes, MD
- 93 Dana R. Levin, MD
- 94 Catherine J. O’Leary, MD
- 95 Katherine E. Stuart, MD
- 96 Ghan B. Thapa, MD
- 97 Aditya Tiwari, MD
- 98 Jared L. Velgersdyk, MD
- 99 Ken Zafren, MD
- 100 Buddha Basnyat, MD (*buddha.basnyat@ndm.ox.ac.uk*)
- 101
- 102
- 103 1 Lipman GS, Hackett P. In response to ibuprofen vs acetaminophen in AMS prevention by  
 104 Kanaan et al. *Wilderness Environ Med.* In press.
- 105 2 Kanann NC, Peterson AL, Pun MI, et al. Prophylactic acetaminophen or ibuprofen result in  
 106 equivalent acute mountain sickness incidence at high altitude: a prospective  
 107 randomized trial. *Wilderness Environ Med.* 2017;28:72-79.
- 108 3 Lipman GS, Kanaan NC, Phillips C, et al. Study looking at end expiratory pressure for  
 109 altitude illness decrease (SLEEP-AID). *High Alt Med Biol.* 2015;16:154-161.
- 110 4 Lipman GS, Kanaan NC, Holck PS, et al. Ibuprofen prevents altitude illness: a randomized  
 111 controlled trial for prevention of altitude illness with nonsteroidal anti-inflammatories.  
 112 *Annals of emergency medicine.* 2012; 59(6):484-90

- 113 5 Gertsch JH, Corbett B, Holck PS, et al: Altitude Sickness in Climbers and Efficacy of NSAIDs  
114 Trial (ASCENT): randomized, controlled trial of ibuprofen versus placebo for prevention  
115 of altitude illness. *Wilderness Environ Med.* 2012; 23:307-315.
- 116 6 Gertsch JH, Lipman GS, Holck PS, et al: Prospective, double-blind, randomized, placebo-  
117 controlled comparison of acetazolamide versus ibuprofen for prophylaxis against high  
118 altitude headache: the Headache Evaluation at Altitude Trial (HEAT). *Wilderness*  
119 *Environ Med.* 2010; 21:236-243.
- 120 7 Gertsch JH, Basnyat B, Johnson EW, et al: Randomised, double blind, placebo controlled  
121 comparison of ginkgo biloba and acetazolamide for prevention of acute mountain  
122 sickness among Himalayan trekkers: the prevention of high altitude illness trial (PHAIT).  
123 *BMJ.* 2004 328:797-799.
- 124 8 Basnyat B, Gertsch JH, Johnson EW, Castro-Marine E, Inoue Y, Yeh C.  
125 Efficacy of Low-dose Acetazolamide (125 mg BID) for the prophylaxis of Acute Mountain Sickness:  
126 A Prospective, Double-blind, Randomized, Placebo-controlled Trial. *High Alt Med Bio.* 2003;  
127 4(1):45-52.
- 128