

Advances in the available non-biological pharmacotherapy prevention and treatment of acute mountain sickness and high altitude cerebral and pulmonary oedema

Joyce, K. E.; Lucas, S. J.E.; Imray, C. H.E.; Balanos, G. M.; Wright, A. D.

DOI:

[10.1080/14656566.2018.1528228](https://doi.org/10.1080/14656566.2018.1528228)

License:

Other (please specify with Rights Statement)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Joyce, KE, Lucas, SJE, Imray, CHE, Balanos, GM & Wright, AD 2018, 'Advances in the available non-biological pharmacotherapy prevention and treatment of acute mountain sickness and high altitude cerebral and pulmonary oedema', *Expert Opinion on Pharmacotherapy*, vol. 19, no. 17, pp. 1891-1902.
<https://doi.org/10.1080/14656566.2018.1528228>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Checked for eligibility: 24/10/2018

This is an Accepted Manuscript of an article published by Taylor & Francis in Expert Opinion on Pharmacotherapy on 11/10/2019, available online: <http://www.tandfonline.com/10.1080/14656566.2018.1528228>.

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

1 **Advances in the available non-biological pharmacotherapy treatment of acute**
2 **mountain sickness and high altitude cerebral and pulmonary oedema**

3
4 **Abstract:**

5
6 ***Introduction***

7 The physiologic responses on exposure to high altitude are relatively well known, but new
8 discoveries are still being made, and novel prevention and treatment strategies may arise. Basic
9 information has changed little since our previous review in this journal ten years ago, but
10 considerable more detail on standard therapies, and promising new approaches are now
11 available.

12 ***Areas covered***

13
14 The role of pharmacological agents in preventing and treating high altitude illnesses is reviewed.
15 The authors have drawn on their own experience and that of international experts in this field.
16 The literature search was concluded in March 2018.

17
18 ***Expert opinion***

19 Slow ascent remains the primary prevention strategy , and rapid descent for management of
20 serious altitude illnesses . Pharmacologic agents are particularly helpful when rapid ascent
21 cannot be avoided or when rapid descent is not possible. Acetazolamide remains the drug of
22 choice for prophylaxis of acute mountain sickness (AMS); however, evidence indicates that
23 reduced dosage schemes compared to the current recommendations are warranted. Calcium
24 channel blockers and phosphodiesterase inhibitors remain the drugs of choice for management of
25 high altitude pulmonary oedema. Dexamethasone should be reserved for the treatment of more
26 severe cases of altitude illnesses such as cerebral oedema.

27
28 **Keywords:** acetazolamide, acute mountain sickness, dexamethasone, high altitude, high altitude
29 cerebral oedema, high altitude pulmonary oedema, nifedipine

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23

1. Introduction

The ease of accessing high altitude above 2000 m presents an opportunity to gain a greater insight into the acute responses to hypoxia [1, 2]. In this review, advances in the pharmacologic prevention and treatment of high altitude illnesses are discussed, aiming to: 1) evaluate currently used pharmacotherapies and 2) consider theoretical pharmacotherapies in light of new discoveries. The following databases were searched (inception March 1) for relevant studies focusing largely on literature produced after 2008: MEDLINE, PubMed, and Embase. Search strategies utilized a set of keywords (with synonyms and closely related words) specific to each section herein with additional studies identified by examining the reference list contained from chosen studies.

The hypobaric hypoxic conditions at altitude elicit distinct temporary and reversible physiologic responses in lowlanders who have spent a few hours to days at high altitude (generally over 3,000 m). These responses are predominantly attributed to hypoxemia [3, 4]. The initial physiologic acclimatisation is hyperventilation, which negates reductions in the partial pressure of oxygen (PO₂) but also results in a greater loss of carbon dioxide (CO₂) (hypocapnia) and subsequent respiratory alkalosis [5]. This respiratory alkalosis elicits a renal compensation response by which the kidneys increase bicarbonate (HCO₃⁻) excretion and increase hydrogen (H⁺) retention, resulting in a secondary metabolic acidosis and a mild diuretic effect [6, 7]. Hypoxia also elicits an increase in sympathetic tone, an increase in blood pressure (BP), and an

1 elevation in resting heart rate (HR) [8]. The magnitude of the response to hypoxia varies
2 considerably between individuals [9].

4 **2. Pathophysiology of High Altitude Illnesses**

5 Three altitude illnesses and their mechanisms are reviewed: 1) acute mountain sickness
6 (AMS), 2) high altitude cerebral oedema (HACE), and 3) high altitude pulmonary oedema
7 (HAPE).

9 **2.1 Acute Mountain Sickness (AMS)**

10 The clinical presentation of AMS includes; headache, gastrointestinal distress, fatigue,
11 and dizziness/lightheadedness [10]. The severity of AMS is determined by an overall symptom
12 score, as an objective measure has yet to be determined. The maladaptive physiologic responses
13 to hypoxia among those who present with AMS have been demonstrated and are different from
14 those who remain free of AMS [11]. The pathophysiology includes: mild fluid retention,
15 increased sympathetic drive, increased cerebral venous volume, reduced cerebrospinal fluid
16 absorption, reduced intracranial buffering capacity, and cognitive impairment [12, 13].

17 Cerebral vasodilation occurs in an attempt to increase oxygenation via an increase in
18 cerebral blood flow [12]. These elevations are normal in the acute exposure phase , returning to
19 baseline after a few days at the same altitude [14]. In some individuals, however, these
20 intracranial dynamics do not return to baseline and progressive increases in intracranial pressure
21 are exhibited, particularly, if the hypoxemia stimulus is maintained in a progressive and
22 aggressive ascent [15].

23

2.2 *High Altitude Cerebral Oedema (HACE)*

AMS and HACE probably occur along a continuum. HACE, a type of encephalopathy with neurological findings, such as, ataxia, altered mental status, and unconsciousness, is potentially fatal. [10]. The causes for the progression of AMS to HACE are unclear; however, current hypotheses attribute such progression to: 1) disruptions in the blood brain barrier (BBB); 2) intracellular oedema, and 3) venous outflow obstruction [15, 16, 17, 18].

Disruptions in the BBB are multifactorial and include: 1) over production of reactive oxygen species (ROS); 2) altered cytokine expression, and/or 3) increased vascular endothelial growth factor (VEGF) [16, 19, 20]. The intracellular oedema aspect of the progression of high altitude cerebral illness has been demonstrated on MRI scans increases in brain parenchymal volumes being associated with increasing Lake Louise Scores [21]. Reductions in venous outflow preceded by an increase in cerebral inflow in response to hypoxia are likely a cause for the progression of cerebral-related altitude illnesses [21]. Vessel deformation may occur within various levels within the brain to include the intracranial and extracranial levels; however, more recent works have demonstrated that vessel deformation at the intracerebral level may be most closely related to the development and progression of cerebral altitude illnesses [18, 21, 22, 23, 24]. The over expression of corticotropin releasing factor may also be a contributor [25].

2.3 *High Altitude Pulmonary Oedema (HAPE)*

Pulmonary arterial pressure (PAP) rises with exposure to altitude, being attributed to hypoxic pulmonary vasoconstriction (HPV). An exaggerated elevation in PAP contributes to the development of alveolar capillary leakage and subsequent development of HAPE [26, 27]. Potential mechanisms include: 1) inflammation, 2) altered alveolar fluid clearance, and/or 3)

1 uneven HPV response [26, 27, 28]. Accumulation of lung fluid in response to hypoxia has been
2 attributed to the downregulation of epithelial sodium channels (ENaC) [29, 30]. Further, greater
3 endothelin-1 production and reduced exhaled nitric oxide are also apparent in those who develop
4 HAPE [31, 32, 33, 34].

5

6 **3. Established Pharmacotherapies for Prevention and Treatment AMS and HACE**

7 Pharmacologic strategies are secondary to immediate descent for the treatment of
8 serious altitude illness (HACE and HAPE). If available, temporary supplemental O₂ to raise
9 oxygen saturation to >90%, or immersion in a portable hyperbaric chamber, are effective
10 treatment strategies. Otherwise, the following pharmacologic approaches should be considered.

11

12 ***3.1 Carbonic Anhydrase Inhibitors***

13 Carbonic anhydrase inhibitors (CAIs) were one of the first pharmacologic agents used to
14 prevent AMS by promoting a preemptive and favorable acclimatization response [35]. Renal CA
15 inhibition, vascular endothelial CA inhibition, erythrocyte CA inhibition, and CNS CA inhibition
16 appear to be the four primary attributes that are most helpful in the prophylactic treatment of
17 AMS [36]. Renal CA inhibition stimulates the loss of bicarbonate (HCO₃⁻) and sodium (Na⁺) in
18 the urine and the subsequent retention of H⁺ and chloride (Cl⁻), effectively reducing serum pH
19 and promoting a state of metabolic acidosis that ultimately stimulates ventilation to equilibrate
20 pH [37, 38].

21 Vasoregulation is also altered with the administration of CAIs via the alteration of
22 extracellular pH, as well as, the direct inhibition of CA in vascular smooth muscle [39]. It
23 should be noted, however, that the peripheral vasculature, pulmonary vasculature, and cerebral

1 vasculature respond differently and/or independently in response to certain drugs [40]. For
2 example, altitude sleep studies have demonstrated the specific influence of CAIs on
3 cerebrovascular reactivity and the subsequent affect on cerebral blood flow [41, 42].

4 5 *3.1.1 Acetazolamide*

6 Acetazolamide (Az) is often used for prophylaxis of altitude illnesses, increasing
7 ventilation and increasing PaO₂ [43, 44, 45, 46]. Off-target effects include: aquaporin
8 inhibition, ROS modulation, heat shock protein-70 (HSP-70) and IL-1 receptor agonist, HIF
9 modulation, and cAMP regulation [36]. Oral administration of Az is more advantageous than
10 intravenous (i.v.) administration at altitude due to its easier administration, as well as, the
11 resultant effects on periodic breathing during sleep at altitude and less reductions in CO₂
12 sensitivity compared with i.v. administration [47, 48].

13 Of more recent concern has been the potential negative effect of Az on exercise
14 performance in hypoxic conditions [49, 50, 51]. The negative effect of Az on performance is
15 particularly apparent in the most recent study which demonstrates the magnitude of performance
16 decrements by quantifying reductions in diaphragm contractility ($18 \pm 10\%$) and joint torques
17 ($39 \pm 11\%$) associated with the drug [51]. It is speculated that exercise performance in older
18 participants may be affected to a greater extent due to reduced renal clearance of Az associated
19 with age-related declines in kidney function [49]. The mechanism by which Az impairs exercise
20 performance is unknown, but such effects should be considered when older subjects are using Az
21 and the maintenance of exercise performance at high altitude is a priority.

22 The side effects of Az for the specific treatment of altitude illnesses include: paresthesia,
23 polyuria, rash, dysgeusia, and increased frequency of micturition [36, 52, 53]. While the side

1 effects are not uncommon and range in severity, paresthesia appears to be the most common
2 [54]. However, such side effects can become severe and appear to relate to increases in dosages
3 in this way [55]. Therefore, it will be important to establish the most effective minimal dose that
4 can be used in order to reduce adverse events [55].

5 A consensus for the time course of administration and dosage of Az has not been met,
6 although guidelines for such applications do exist [56]. The dose of Az for AMS prophylaxis
7 has been recommended at 125 mg – 250 mg twice daily (BID), initiating administration the day
8 prior to altitude exposure; however, recent data suggest pre-treatment with low-dose Az (125 mg
9 BID) should be initiated 2 days prior to exposure to altitude [52, 53, 57]. Studies concerning the
10 effective dosage regimens of Az while at altitude provide evidence favouring reductions in
11 dosage schemes [58, 59, 60]. Even lower dosages of 62.5 mg BID can be as effective in
12 preventing AMS [59]. Hypoxia and, possibly, additional environmental stressors imposed by
13 high altitude exposure may alter drug pharmacokinetics, particularly, in drugs such as Az and,
14 thus, may reduce the clearance of such drugs [61]. Furthermore additional research is warranted
15 to determine the individualization of Az dosing.

16

17 *3.1.2 Methazolamide*

18 Methazolamide (Mtz) may incur less side effects than Az, as it is less bound to plasma
19 proteins and diffuses more readily into tissues [62]. Comparative studies have demonstrated that
20 Mtz administration of 150 mg is equally effective as Az in preventing AMS with less paresthesia
21 [63]. Additionally, Mtz may elicit less performance decrements compared to Az [51]. The
22 differences in the pharmacodynamics of the drugs and their side effects or maybe responsible for
23 the disparities among the magnitude of effects elicited.

1 Comparative studies of Az and Mtz show that when CA is fully inhibited, different
2 effects may be a consequence of the off-target effects of the medications [64]. The magnitude of
3 the hypoxic-ventilatory response is far less with Az than with Mtz [64]. In vitro, Mtz but not Az
4 activates the gene transcription factor nuclear related factor 2 (Nrf-2), which is responsible for
5 the upregulation of antioxidant proteins that serve a primary purpose of scavenging reactive
6 oxygenated species (ROS); however, it is unclear if these effects will translate to the whole
7 organism [65]. Early speculations of ROS involvement in the development of AMS have been
8 supported by evidence demonstrating the importance of the balance of ROS production and ROS
9 scavenging for the prevention of AMS [66]. Thus, it could be argued that the proper
10 management of ROS with high altitude exposure is critical for the prevention of altitude
11 illnesses, specifically, in those persons with a genetic profile that is indicative of hyperactive
12 ROS production. Further, research is needed in order to evaluate the efficacy of various CAIs
13 for the prophylactic treatment of altitude illnesses based on genetic profiles and in relation to
14 ROS production.

15

16 *3.1.3 Benzolamide*

17 Benzolamide (Bz) has been compared with Az for prophylactic treatment of AMS [67].
18 Significantly lower AMS scores were obtained on Bz when compared to Az, particularly at
19 higher elevations [68]. The effects of Bz and Az at altitude, such as, increased urinary pH and
20 volume, as well as, increased arterial oxygenation, appear to be similar between the two drugs
21 [68, 69]. Bz has been shown to have reduced psychomotor effects compared to Az, indicating
22 that Bz may penetrate the central nervous system (CNS) tissue less than Az. Furthermore, due to

1 its more limited tissue penetrance and near isolated effects on renal CA, Bz elicits fewer CNS-
2 related side effects [38, 68].

3

4 **3.2 Corticosteroids**

5 *3.2.1 Dexamethasone (Dx)*

6 Recent reviews have highlighted the effects of Dx in its ability to prevent altitude
7 illnesses, which include: reductions in ROS formation, endogenous antioxidant upregulation,
8 sympatholysis, improved O₂ saturation, alteration of aquaporin expression, and HSP-70 and
9 adrenomedullin upregulation [36]. However, its use as a prophylactic agent could become
10 problematic for many reasons. Unlike Az, Dx does not permit the normal acclimatization
11 process to transpire. Additionally, if Dx is used as a prophylactic agent and is then abruptly
12 discontinued during ascent, acute illness may set in. For this reason, its use as a prophylactic
13 treatment should be avoided when possible, and other drugs should be considered.

14 The clinical management of HACE is distinctly different. HACE is a medical emergency
15 requiring immediate attention, and is known to occur in those whom have already developed
16 AMS. Early treatment using Dx is the most effective [70]. An initial large dose of Dx is advised,
17 8 – 10 mg by intramuscular or oral administration, followed by 4 mg every 6 hours [56].

18

19 *3.2.2 Inhaled Budesonide*

20 Conflicting results have been produced concerning the efficacy of inhaled budesonide for
21 preventing and treating altitude illnesses. Administration of inhaled budesonide for 3 days prior
22 to ascent has been effective in preventing AMS in the first 20 hours of HA exposure [71].
23 However, more recent research shows no significant reductions in AMS with budesonide

1 administration at various dosages nor has it shown the ability of budesonide to prevent AMS to
2 the same degree as Az [72, 73]. Budesonide is a drug that elicits isolated effects on the lung
3 tissue as opposed to eliciting a systemic effect, thus, its efficacy for the prophylactic treatment of
4 AMS may be limited. [74].

5

6 **3.3 Diuretics**

7 Abnormal fluid balance has been repeatedly observed in those whom present with AMS
8 [75, 76]. While a degree of diuresis with hypoxic exposure is considered a normal response,
9 individuals who develop AMS demonstrate significantly greater fluid retention than those who
10 do not develop AMS [76]. Such diuresis at high altitude is also related to the ventilatory
11 response to hypoxia, such that, a blunted ventilatory response may result in a greater degree of
12 fluid retention and ensuing altitude illness [77, 78, 79, 80, 81]. Furthermore, such blunted
13 responses and associated fluid retention may promote the development of HAPE. Thus, the
14 maintenance of an appropriate fluid balance at high altitude, namely preventing a state of fluid
15 excess, is important for the prevention of all altitude-related illnesses [76, 82]. There is limited
16 information on the use of diuretics in preventing AMS except it has been shown that
17 spironolactone is ineffective in preventing AMS when compared to Az [83]. It is also possible
18 that those with AMS may be volume depleted, thus, the use of a loop diuretic in this instance
19 could be problematic. Herein lies the rationale behind furosemide being deamed as inappropriate
20 for the treatment of AMS which would produce excessive diuresis that may be dangerous at
21 altitude [62]. Spironolactone has also been considered for the treatment of altitude illnesses due
22 to the mild acidosis produced [83].

23

1 **3.4 Angiotensin Converting Enzyme (ACE) Inhibitors**

2 Angiotensin converting enzyme (ACE), found predominantly in the pulmonary and renal
3 endothelia, plays a key role in the renin-angiotensin aldosterone system (RAAS). ACE
4 influences the control of systemic BP via its conversion of angiotensin-I to angiotensin-II (A-II)
5 and the subsequent downstream effects on fluid balance. The implications of ACE and
6 performance at altitude have been evaluated but the use of ACE inhibitors was not addressed
7 [84]. More recent discoveries surrounding genetic polymorphisms of the ACE gene and
8 associated responses to hypoxia have resulted in the consideration of ACE inhibitors for
9 prevention and treatment of altitude illnesses [85, 86]. As individuals with the “DD” genotype
10 appear to be at greater risk for maladaptations at altitude, inducing physiologic response that is
11 more consistent with a favorable II or ID genotype could be advantageous altitude [87].

12 The effects of ACE inhibitors during exposure to hypoxia include blunting of the hypoxic
13 ventilatory response and reduction in PAPs [86, 88, 89]. Therefore, such drugs may reduce
14 HAPE in a similar way to that of nifedipine [86]. However, ACE inhibitors have been shown to
15 blunt the kidneys ability to produce erythropoietin and, thereby, producing an unwanted effect in
16 those attempting to acclimatize [90]. While the ventilatory responses to ACE inhibitors during
17 hypoxia have been briefly considered, further research is warranted in this area. Future research
18 should also consider the hormonal effects of ACE inhibitors with hypoxic exposure, such as the
19 influence on aldosterone and any subsequent relation to altitude illnesses.

20

21 **3.5 Angiotensin-II Receptor Blockers (ARBs)**

22 Intermittent hypoxia such as in sleep apnoea is accompanied by concomitant rises in BP,
23 which may be mediated by A-II [85, 91, 92]. ARBs, such as, telmisartan have been shown to

|

1 reduce increases in BP associated with ascent to altitude up to 3400 m in healthy individuals [93,
2 94, 95]. Additionally, losartan appears to alleviate the oxidative stress imposed by intermittent
3 hypoxia and may reduce ROS production [91]. Thus, ARBs may attenuate the progression of
4 altitude illnesses by regulating fluid volume, reducing altitude associated increases in BP, and
5 alleviating oxidative stress; however, their efficacy at extreme altitudes may be limited [91, 93].
6 Furthermore, ARBs and ACE inhibitors are safe to administer at altitude but comparisons
7 between these drugs and existing pharmacologic strategies, such as Az, are warranted.

8

9 ***3.6 Magnesium***

10 Magnesium is an antagonist of N-methyl-D-aspartate (NMDA). The involvement of the
11 N-methyl-D-aspartate (NMDA) receptor in regards to hypoxic altitude convulsions has
12 previously been implicated with a blockage of the NMDA receptor proving to have beneficial
13 effects [62, 96, 97]. Intravenous magnesium appears to be superior over oral administration for
14 the attenuation of AMS [62, 98, 99]. The precise connection between NMDA and AMS remains
15 unclear and further investigations are needed.

16

17 ***3.7 Ibuprofen and Paracetamol***

18 High altitude headache (HAH) is an important symptom in the recently revised AMS
19 scoring scheme [10]. Conflicting results have been produced regarding ibuprofen's efficacy
20 compared. Ibuprofen has been repeatedly shown to reduce HAH due to its anti-inflammatory
21 effects [100, 101, 102], which may also be responsible for its superiority over paracetamol.
22 Studies have also shown ibuprofen and paracetamol to be equivocal in preventing HAH [103,
23 104].

|

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23

3.8 Nitrovasodilators

The involvement of endothelial nitric oxide synthase (NOS) in the development of altitude illnesses has been outlined [62] and further implicated in those studies observing lowlanders travelling to altitude exhibiting reductions in exhaled NO which have correlated with AMS scores and the presentation of HAPE [32, 33, 105, 106]. Others have argued that exhaled NO decreases with increasing altitude and may not be a contributor to HPV [105, 107]. However, recent studies concerning gene variants of the nitric oxide synthase 3 gene (NOS3), a gene encoding for eNOS, in relation to both, acclimatization and adaptation to altitude are conflicting [108, 109]. Despite, nitrates' ability to improve exercise performance at sea-level, recent findings indicate that dietary nitrate consumption exacerbates AMS symptoms and increases the sense of effort with maximal exercise in hypoxia [110].

4. Established Pharmacotherapies for Prevention & Treatment of HAPE

Despite some overlap, the development of HAPE is attributed to alternative maladaptations compared to AMS and HACE. HPV and the resultant pulmonary hypertension, stress failure of the pulmonary capillaries, and disrupted alveolar fluid clearance have all been hypothesized to contribute to the development of HAPE [4, 111, 112, 113]. While immediate descent remains the first line treatment for HAPE, drugs that act on any one of aforementioned pathways can also be helpful for prevention and treatment.

4.1 Calcium-Channel Blockers (CCBs)

4.1.1 Nifedipine

1 Nifedipine, a calcium channel blocker, interferes with the calcium channel blockade,
2 inhibiting vasoconstriction and reducing PAPs. Administration of 20 mg of slow-release
3 nifedipine every 8 hrs prevents HAPE in those persons whom are known to be susceptible [88].
4 For acute treatment of HAPE, an immediate dosage of 10 mg of nifedipine should be
5 administered sublingually followed by 20 mg every 6 hrs in addition to supplemental oxygen and
6 descent [62, 114].

7

8 ***4.2 Phosphodiesterase Inhibitors (PDE-5 Inhibitors)***

9 Elevated PAPs are of concern in relation to altitude illnesses and can result in the
10 development of HAPE and worsening hypoxemia [115]. Phosphodiesterase inhibitors (PDE-5
11 inhibitors) are of interest for HAPE prevention, due to their ability to attenuate rises in PAPs
12 with ascent. Recent reviews have demonstrated the efficacy of PDE-5 inhibitors, such as
13 tadalafil and sildenafil, for the treatment of elevated PAPs [62, 115, 116, 117]. Pre-treatment
14 with 10 mg of tadalafil has been shown to protect against HAPE (reducing incidence by 78%) in
15 those who are susceptible by attenuating rises in PAP [118]. Newer research is in agreement
16 with these earlier works demonstrating reductions in the incidence of HAPE with tadalafil [119].

17 Although PDE-5 inhibitors are known to improve HPV and, thereby, reduce the
18 propensity for developing HAPE, results regarding the efficacy of PDE-5 inhibitors for
19 prevention and treatment of other altitude illnesses are less conclusive. Sildenafil may be
20 appropriate for AMS and HACE prophylaxis based on its ability to increase cerebral
21 oxygenation [120]. Tadalafil may have the potential to reduce cerebral specific AMS scores;
22 however, it may also increase the potential of headache [111, 119, 121, 122]. Consequently,

1 more research is needed to clarify whether PDE-5 inhibitors can be used to prevent and treat
2 AMS an HACE.

3

4 **4.3 Acetazolamide.**

5 There is evidence that acetazolamide inhibits HPV in many animal models and in humans
6 and, therefore, could be useful in the prevention, and perhaps treatment, of HAPE [123].

7

8 **4.4 Corticosteroids**

9 **4.4.1 Dexamethasone**

10 While the treatment of HACE with Dx is recommended, its administration for the
11 treatment of HAPE is less established. Recent guidelines provide a Recommendation Grade of
12 2C for Dx as a preventative strategy for HAPE due to limited evidence, and suggest that it is
13 reserved for the clinical presentation of HAPE, known HAPE-susceptible individuals, or when
14 alternative therapies are contraindicated [56]. It is possible that Dx could reduce HAPE by
15 stimulating the cGMP production in response to hypoxia, increasing NOS activity and
16 modulating sympathetic activity; however,. limited reports have documented its use in this way
17 [118, 124, 125, 126].

18

19 **4.5 Iron Supplementation**

20 The suggestion of iron supplementation for the treatment of altitude illnesses comes from
21 the effects that severe iron deficiency has on the pulmonary vasculature resulting in pulmonary
22 vasoconstriction [127]. Unfortunately, however, it seems that i.v. iron supplementation has no
23 significant protective effect against AMS [128].

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23

5. Future Pharmacotherapies for Prevention & Treatment of Altitude Illnesses

This next section provides suggestions for the potential use of other pharmacologic agents in preventing and treating altitude illnesses.

5.1 Type A Endothelin Receptor Antagonists (ET_A Receptor Antagonist)

The effects of hypoxia in pulmonary vasculature may be detrimental and result in a greater propensity for apoptosis in the pulmonary artery smooth muscle cells [129]. Thus, susceptibility to altitude-related illnesses attributed to such effects on the pulmonary vasculature should be kept in mind with the consideration of new pharmacotherapies for prevention and treatment of altitude illnesses.

Type A endothelin receptor antagonists (ET_A antagonists) elicit similar outcomes as PDE-5 inhibitors on the pulmonary vasculature, however, the mechanism of action of ET_A antagonists is inherently different. In animal models, ET_A antagonists have proven to be beneficial in reduction of PAPs in the HAPE susceptible [31, 130, 131, 132, 133]. It has also been hypothesized that additional off-target effects of ET_A antagonists may be more beneficial for the prophylactic treatment of altitude illnesses [65].

5.1.1 Sitaxentan

Research has demonstrated that the ET_A antagonist sitaxentan reduces pulmonary vascular resistance (PVR) in both, acute and chronic hypoxia with such changes in PVR being correlated with restorations in VO_{2max} [134]. Increases in PVR associated with hypoxia may be a contributing factor to the reductions in VO_{2max} observed in hypoxia. Thus, sitaxentan, may offer an alternative option to existing pharmacotherapies, especially, when exercise performance

1 at altitude is a priority. *In vivo* models have shown sitaxentan reduces high-altitude induced
2 cerebral vascular leakage by 40% but its effect on altitude illnesses remains uninvestigated [65].

4 5.1.2 Ambrisentan

5 Ambrisentan is currently approved for the treatment of pulmonary arterial hypertension
6 and having limited interactions with other medications [135]. Ambrisentan has been shown to
7 improve exercise capacity and reduce HPV [136, 137]. When compared to sitaxentan,
8 ambrisentan increased Nrf-2 four-fold, helping to scavenge greater amounts of ROS [65].
9 Additionally, *in vitro* studies have shown that ambrisentan decreased hypoxia-induced H₂O₂
10 production and permeability in basal media endothelial cells [65], indicating its potential use for
11 prophylaxis of HAPE [65]. The efficacy of ambrisentan for the specific prevention and
12 treatment of altitude illnesses is unknown.

14 5.1.3 Bosentan

15 Bosentan, also approved for treatment of PAP, has repeatedly been shown to reduce
16 increases in PAP associated with altitude exposure in animals, healthy humans and known HAPE
17 susceptible individuals [132, 138]. However, bosentan may have adverse effects on renal
18 adaptation at high altitude, specifically, reducing diuresis [139]. This could present as
19 problematic with ascent to altitude in light of the known relationship between reductions in
20 diuresis and a greater propensity for developing altitude illnesses [140, 141].

22 5.14 Macitentan

1 Macitentan is an ET_A antagonist indicated for the treatment of PAH [142]. Macitentan
2 improves PAP and exercise capacity, so may attenuate the development of altitude illnesses
3 [143, 144]. Due to the effects of altitude and the associated hypobaric hypoxic conditions that
4 elicit a disruption in the vasoregulatory processes and promote vasoconstriction, caution should
5 be taken with drugs that may attenuate the vasoconstriction response and favorably affect PAP
6 (see below). The vasoregulatory changes and vascular characteristic changes (reduced capillary
7 density and diameter) induced by hypoxia appear to be attenuated with macitentan in healthy
8 individuals in hypobaric hypoxic conditions [143]. Thus, macitentan could attenuate the
9 development of altitude illnesses by improving capillary blood flow, and microcirculation [143],
10 and attenuating the hypoxia-induced rise in PAPs.

11

12 ***5.2 IL-10 Upregulators***

13 Gene connectivity has been used to evaluate the connections between AMS (from high
14 altitude exposure) and genetic profiles [145]. Early research revealed that HAPE is largely
15 attributed to a failure of the lung endothelial lining due to high intravascular pressures rather than
16 inflammation, with this lining failure a more likely source of such vascular leak [36, 80]. These
17 earlier studies appear not to draw attention to the potential effect of the anti-inflammatory
18 involvement in the prevention of altitude illnesses though such an approach has been proposed
19 recently [146, 147].

20 Liu et al. [145] has highlighted the genetic profiles of those with AMS compared to those
21 without AMS during altitude exposure, revealing a contrast in the production of anti-
22 inflammatory cytokines between AMS non-AMS groups. More specifically, Liu et al. [145] was
23 able to isolate the change in interleukin (IL) gene expression amongst those with AMS who

1 presented with a downregulation of IL-2, IL-4, IL-6ST, IL-7, IL-10, IL-17B, and IL-32, as well
2 as, an upregulation in IL-13 and IL-17F. Others have further implicated the involvement of
3 endothelin 1 (ET-1), IL-6, and IL-17a [148]. Liu et al. [145] further analysed differential
4 connectivity patterns among gene expressions across groups, and found that IL-10 and CCR7
5 were substantially downregulated and IL-17F and CCL8 were substantially upregulated in the
6 AMS group. This could be due to an enriched DUSP1 response to oxidative stress at altitude,
7 limiting the IL-10 production by adversely effecting p38 phosphorylation [145]. An additional
8 mechanism [145] is the downregulation of the CCR7 protein, a protein that maintains T-cell
9 function normal secretion of IL-10. Based on these findings there is substantial evidence
10 implicating the involvement of the inflammatory response (anti-inflammatory response) in the
11 development of AMS. This evidence also supports the consideration of alternative
12 pharmacologic agents that promote IL-10 upregulation for the prevention and treatment of
13 altitude illnesses.

14

15 *5.2.1 Gabapentin*

16 The use of alternative drugs that influence the upregulation of IL-10 may be more
17 appropriate as prophylactic agents. Gabapentin has been used to treat high altitude headache and
18 is now known to upregulate IL-10; however, the use of gabapentin to treat altitude illnesses has
19 not gained wide popularity [132, 149, 150, 151].

20 **5.3 Rho-kinase Inhibitors**

21 *5.3.1 Fausidil*

22 At high altitude, hypoxia-induced pulmonary hypertension is one of the physiologic
23 factors that can result in HAPE and reduced cardiopulmonary performance [80, 152]. The rho-

1 kinase inhibitor fasudil reduces high-altitude pulmonary hypertension with high-altitude
2 exposure [153]. Rho-kinase inhibitors in combination with ARBs reduce proteinuria by helping
3 to maintain the podocyte integrity, thereby protecting the kidneys [154]. Overall, the efficacy of
4 rho-kinase inhibitors and their use in the prophylactic treatment for high-altitude illnesses is
5 relatively unknown.

6

7 ***5.4 Guanylate Cyclase Stimulators***

8 ***5.4.1 Riociguat (Adempas)***

9

10 A contribution of the rho-kinase signaling pathway to the development of HAPE has
11 been suggested. Riociguat (Adempas) could be a novel treatment for HAPE, specifically in those
12 whom are at an increased risk for developing HAPE based on their genetic profile [155].
13 Riociguat decreases pulmonary vascular resistance while increasing cardiac output and
14 peripheral O₂ delivery during rest and low intensity exercise at simulated altitude (15000 ft.)
15 [156]. Furthermore, no changes in VO_{2max} were reported with riociguat administration. This is
16 promising in view of recent research with concern for the potential cardiovascular effects and
17 exercise performance limitations amongst older individuals (e.g. 50+ years) [49]. The efficacy
18 for the use of riociguat as a prophylactic agent against AMS or HAPE is unknown.

19

20 ***5.5 Oxyhaemoglobin Dissociation Influencers***

21 Inducing a leftward shift in the oxyhaemoglobin dissociation curve could potentially
22 help prevent or reduce the risk of altitude illnesses [157].

23

1 *5.5.1 GBT1118 and GBT 440*

2 GBT1118, an O₂-hemoglobin (Hb-O₂) affinity modulator via an allosteric change to
3 haemoglobin, has been demonstrated to have favourable effects on the oxyhaemoglobin
4 dissociation curve [158]. It reduces hypoxemia by increasing arterial oxygenation in hypoxemic
5 animals [158]. GBT1118 also reduces leukocyte infiltration into the lungs and prevents
6 pulmonary inflammation in hypoxemic animals [158]. GBT440 induces a favourable shift,
7 similar to GBT440, under conditions that mimic strenuous exercise, hypoxia, and acidosis [159].

8

9 ***5.6 Corticotropin-releasing Factor Antagonists***

10 Corticotropin-releasing hormone (CRH), is a peptide hormone released from the
11 hypothalamus in response to stress resulting in the release of ACTH. CRH has been shown to
12 contribute to the brain-endocrine-immune network and associated dysfunction in altitude illness
13 [160]. Individuals that with AMS demonstrate enhanced plasma levels of CRH in response to
14 hypoxia induced by rapid ascent [161]. It is possible that enhanced plasma levels of CRH, which
15 activate the cAMP-dependent protein kinase pathway and calcium influx through L-type
16 channels, contributes to excessive vasoconstriction in response to hypoxia, thereby, promoting
17 AMS [161]. Over activation of the target receptor of CRH, the corticotropin releasing hormone
18 receptor-1 (CRHR1) in response to hypoxia has also been shown to contribute to increased
19 expression of aquaporin-4 (increasing cellular permeability), promoting cellular water influx and
20 cerebral oedema [25]. Therefore, drugs that block or produce antagonistic effects at the CRHR1
21 receptor may attenuate this hypoxic response .

22

23 *5.6.1 CP154,526*

1 CP154,526 is a CRHR1 antagonist, negating the effects of CRH. CP154,526 appears to
2 reduce the hypoxia-associated increases in pro-inflammatory markers, such as TNF- α and IL-1 β ,
3 which correlate AMS [162]. It is possible that CP154,526 may reduce the stress response
4 associated with hypoxia and reduce the incidence of AMS. Future research is warranted for the
5 efficacy in altitude illness of CRHR1 antagonists such as antalarmin and pexacerfont in addition
6 to CP154,526.

7

8 **5.7 Nootropics**

9 *5.7.1 Oxiracetam*

10 Oxiracetam has been reported to influence brain function at high altitude. Blood flow
11 velocity measured by transcranial Doppler decreased in both anterior and posterior circulations
12 following the administration of oxiracetam, attributed to vasodilation in the posterior and
13 anterior circulation [163]. More importantly preconditioning with oxiracetam appeared to reduce
14 the decline in cognitive function on ascent to altitude.

15

16 **5.8 Glutathione S-transferase Inducers**

17 Decreases in plasma glutathione S-transferase activity have been associated with the
18 presentation of AMS, with specific glutathione S-transferase genes being independently
19 associated with AMS [164, 165, 166]. Compounds that induce glutathione S-transferase activity
20 may protect against oxidative stress and need to be investigated in the prevention of AMS [167,
21 168]. Interestingly, the Chinese herbal treatment *Cordyceps sinensis*, unique to the Sikkim region
22 of the Himalayas, has been shown to increase glutathione stimulating hormone, inducing heme

1 oxygenase-1, and metallothionein (via activation of Nrf-2), which may increase hypoxic tolerance
2 [169].

4 **6. Conclusion**

5 The evolving understanding of pathophysiologies associated with altitude has enabled for
6 a more thorough evaluation of existing pharmacotherapies used to prevent and treat altitude
7 illnesses and has allowed for the consideration of alternative options. When rapid ascent is
8 unavoidable, and immediate descent is impossible, established pharmacotherapies remain
9 important for preventing and managing altitude-related illnesses. Additional alternative agents
10 presented here offer a considerable expansion of existing pharmacotherapies for the future.

12 **7. Expert opinion**

13 The spectrum of acute altitude illnesses range from mild, self-limiting syndromes of
14 AMS and HAH, to more severe syndromes, such as HACE and HAPE. Pathophysiologic
15 changes that contribute to the development of AMS occur on a continuum with HACE, and thus,
16 treatment and prevention strategies for these acute altitude illnesses also occur along this
17 continuum. On the other hand, HAPE is attributed to an alternate pathophysiologic responses
18 and pharmacological treatments.

19 Slow ascent remains the primary prevention strategy for the development of altitude
20 illness, and rapid descent remains the primary treatment strategy for all altitude illness.
21 Pharmacologic agents aid in both the prevention and treatment of such illnesses. Pharmacologic
22 agents are particularly helpful when rapid ascent cannot be avoided or rapid descent is not
23 possible. Strikingly, after decades of research, these pharmacologic prevention and treatment

1 strategies have not changed wildly. Acetazolamide remains the pharmacologic agent of choice
2 for the prevention and treatment of AMS and HACE and appears to be effective in dosages as
3 little as 62.5 mg twice daily for prevention. Consideration should be given when prescribing
4 Az to adults over the age of 50 given the age-related reductions in kidney function and therefore
5 lower renal clearance of Az. Calcium-channel blockers and PDE-5 inhibitors remain the
6 pharmacologic agents of choice in the prevention and treatment of HAPE. Dexamethasone is
7 inappropriate for prophylaxis and should be reserved for the treatment of HACE.
8 Dexamethasone's efficacy for the treatment of HAPE remains unestablished; however, it should
9 not be forfeited as a treatment option in this instance entirely, particularly, when alternative
10 treatment strategies may be contraindicated.

11 In light of the research advances that have been made in the last 10 years, current
12 evidence supports the potential inclusion of alternative and newer drugs for the prevention and
13 treatment of altitude illnesses. IL-10 upregulators may be helpful in preventing all altitude
14 related illnesses and particularly AMS. Corticotropin-releasing factor antagonists, glutathione S-
15 transferase inducers and nootropics may be beneficial for prophylaxis and treatment of AMS,
16 specifically. Type A endothelin receptor antagonists, rho-kinase inhibitors, and guanylate
17 cyclase stimulators may serve as additive or alternative agents for prophylaxis and treatment of
18 HAPE. Agents that influence the oxyhaemoglobin dissociation curve may be beneficial in
19 preventing and treating all altitude illnesses. Further evaluation of the efficacy of these newer
20 treatment strategies is warranted.

21 Identification of those who are susceptible to altitude illnesses, as well as gaps in the
22 existing knowledge regarding the etiology of the development of these illnesses, are challenges
23 for the future. Ideally, an objective measure of AMS is required in addition to the Lake Louise

1 scoring system widely used in research studies. While the pharmacologic prevention and
2 treatments strategies discussed herein are warranted, future research should aim to elucidate the
3 importance of including genetic profiling prior to prescribing medication for those patients
4 wishing to sojourn to high altitude. Genetic profiling in this instance would allow for the
5 evaluation of gene expression and expression patterns that are consistent with (or may contribute
6 to the development of) those who have previously been observed to develop altitude illnesses.
7 This would allow not only for a risk evaluation and determination of susceptibility prior to
8 sojourn, but would also allow for the appropriate prescription of pharmacologic agents ..
9 Therefore, future pharmacologic research pertaining to the prevention and treatment of high
10 altitude medicine should be largely focused on personalized medicine and/or combination
11 treatments for the best outcomes.

12 **Article highlights box**

- 13 • Pathophysiology of altitude illnesses is outlined.
- 14 • Existing pharmacotherapies for prevention and treatment of AMS, HACE, and HAPE are
15 discussed.
- 16 • Off-label pharmacotherapies for prevention and treatment AMS, HACE, and HAPE are
17 presented.
- 18 • Updated concensus regarding pharmacologic prevention and treatment of altitude
19 illnesses is given.
- 20 • Focus of future research for the pharmacologic prevention and treatment of altitude
21 illnesses is suggested.

22 23 ***Acknowledgments***

1 We are grateful for the support of Professor A. R. Bradwell and the Birmingham Medical
2 Research Expeditionary Society.

- 3
- 4 1. Levine BD, Zuckerman JH, deFilippi CR. Effect of high-altitude exposure in the elderly:
5 the Tenth Mountain Division study. *Circulation*. 1997 Aug 19;96(4):1224-32.
- 6 2. Honigman B, Theis MK, Koziol-McLain J, et al. Acute mountain sickness in a general
7 tourist population at moderate altitudes. *Ann Intern Med*. 1993;118(8):587-592.
- 8 3. Hackett PH, Roach RC. High-altitude illness. *N Engl J Med*. 2001 Jul 12;345(2):107-14.
- 9 4. Bartsch P, Swenson ER. Acute high-altitude illnesses. *N Engl J Med*. 2013 Oct
10 24;369(17):1666-7.
- 11 5. West JB. Human responses to extreme altitudes. *Integr Comp Biol*. 2006 Feb;46(1):25-34.
- 12 6. Koller EA, Buhner A, Felder L, et al. Altitude diuresis: endocrine and renal responses to
13 acute hypoxia of acclimatized and non-acclimatized subjects. *Eur J Appl Physiol Occup Physiol*.
14 1991;62(3):228-34.
- 15 7. Heyes MP, Farber MO, Manfredi F, et al. Acute effects of hypoxia on renal and
16 endocrine function in normal humans. *Am J Physiol*. 1982 Sep;243(3):R265-70.
- 17 8. Heistad DD, Abboud FM, Dickinson W, Richards Lecture: Circulatory adjustments to
18 hypoxia. *Circulation*. 1980 Mar;61(3):463-70.
- 19 9. Burtcher M, Flatz M, Faulhaber M. Prediction of susceptibility to acute mountain
20 sickness by SaO₂ values during short-term exposure to hypoxia. *High Alt Med Biol*. 2004
21 Fall;5(3):335-40.
- 22 **10. Roach R, Hackett P, Oelz O, et al. The 2018 Lake Louise Acute Mountain Sickness
23 Score. *High Alt Med Biol*. 2018;0(0):1-3.
24 The most up to date version of the Lake Louise Scoring System of which parameters have
25 updated since the previous expert opinion in pharmacotherapy regarding prevention and
26 treatment of altitude illnesses. Sleep scores have changed/removed which may influence
27 existing correlations between therapeutic outcomes (of established pharmacotherapies) and AMS
28 scores.
- 29 11. Imray C, Wright A, Subudhi A, et al. Acute mountain sickness: pathophysiology,
30 prevention, and treatment [Review]. *Progress in cardiovascular diseases*. 2010 May-
31 Jun;52(6):467-84.
- 32 12. Pearce WJ. Mechanisms of hypoxic cerebral vasodilatation. *Pharmacol Ther*. 1995
33 Jan;65(1):75-91.
- 34 13. Phillips L, Basnyat B, Chang Y, et al. Findings of Cognitive Impairment at High Altitude:
35 Relationships to Acetazolamide Use and Acute Mountain Sickness. *High Alt Med Biol*.
36 2017;18(2):121-127.
- 37 14. Lucas SJE, Burgess KR, Thomas KN, et al. Alterations in cerebral blood flow and
38 cerebrovascular reactivity during 14 days at 5050 m. *J Physiol*. 2011;589(3):741-753.
- 39 15. Lawley JS, Levine BD, Williams MA, et al. Cerebral spinal fluid dynamics: effect of
40 hypoxia and implications for high-altitude illness. *J Appl Physiol* (1985). 2016 Jan
41 15;120(2):251-62.
- 42 16. Davis C, Hackett P. Advances in the Prevention and Treatment of High Altitude Illness.
43 *Emerg Med Clin North Am*. 2017 May;35(2):241-260.

- 1 17. Willmann G, Gekeler F, Schommer K, et al. Update on high altitude cerebral edema
2 including recent work on the eye. *High Alt Med Biol.* 2014 Jun;15(2):112-22.
- 3 18. Wilson MH, Newman S, Imray CH. The cerebral effects of ascent to high altitudes.
4 *Lancet Neurol.* 2009 Feb;8(2):175-191.
- 5 19. Himadri P, Kumari SS, Chitharanjan M, et al. Role of oxidative stress and inflammation
6 in hypoxia-induced cerebral edema: a molecular approach. *High Alt Med Biol.* 2010
7 Fall;11(3):231-44.
- 8 20. Schoch HJ, Fischer S, Marti HH. Hypoxia-induced vascular endothelial growth factor
9 expression causes vascular leakage in the brain. *Brain.* 2002 Nov;125(Pt 11):2549-57.
- 10 *21. Sagoo RS, Hutchinson CE, Wright A, et al. Magnetic Resonance investigation into the
11 mechanisms involved in the development of high-altitude cerebral edema. *J Cereb Blood Flow*
12 *Metab.* 2017;37(1):319-331.
13 Significant contribution to the understanding AMS and HACE pathophysiology. Demonstrates
14 an association with increases in white matter and Lake Louise Scores.
- 15 22. Willmann G, Fischer MD, Schommer K, et al. Missing correlation of retinal vessel
16 diameter with high-altitude headache. *Ann Clin Transl Neurol.* 2014 Jan;1(1):59-63.
- 17 23. Wilson MH, Davagnanam I, Holland G, et al. Cerebral venous system and anatomical
18 predisposition to high-altitude headache. *Ann Neurol.* 2013 Mar;73(3):381-9.
- 19 24. Wilson MH, Imray CH. The cerebral venous system and hypoxia. *J Appl Physiol* (1985).
20 2016 Jan 15;120(2):244-50.
- 21 25. Chen SJ, Yang JF, Kong FP, et al. Overactivation of corticotropin-releasing factor
22 receptor type 1 and aquaporin-4 by hypoxia induces cerebral edema. *Proc Natl Acad Sci U S A.*
23 2014 Sep 9;111(36):13199-204.
- 24 *26. Luks AM, Swenson ER, Bartsch P. Acute high-altitude sickness. *Eur Respir Rev.* 2017
25 Jan;26(143).
26 Updated review highlighting the clinical presentations that are consistent with each of the altitude
27 illnesses: acute mountain sickness, high altitude cerebral oedema, and high altitude pulmonary
28 oedema.
- 29 27. Bartsch P, Mairbaurl H, Maggiorini M, et al. Physiological aspects of high-altitude
30 pulmonary edema. *J Appl Physiol* (1985). 2005 Mar;98(3):1101-10.
- 31 28. Dehnert C, Mereles D, S. G, et al. Exaggerated hypoxic pulmonary vasoconstriction
32 without susceptibility to high altitude pulmonary edema. *High Alt Med Biol.* 2015;16(1):11-17.
- 33 29. Egli M, Duplain H, Lepori M, et al. Defective respiratory amiloride-sensitive sodium
34 transport predisposes to pulmonary oedema and delays its resolution in mice. *J Physiol.* 2004
35 Nov 1;560(Pt 3):857-65.
- 36 30. Matthay MA, Folkesson HG, Verkman AS. Salt and water transport across alveolar and
37 distal airway epithelia in the adult lung. *Am J Physiol.* 1996 Apr;270(4 Pt 1):L487-503.
- 38 31. Sartori C, Vollenweider L, Loffler BM, et al. Exaggerated endothelin release in high-
39 altitude pulmonary edema. *Circulation.* 1999 May 25;99(20):2665-8.
- 40 32. Busch T, Bartsch P, Pappert D, et al. Hypoxia decreases exhaled nitric oxide in
41 mountaineers susceptible to high-altitude pulmonary edema. *Am J Respir Crit Care Med.* 2001
42 Feb;163(2):368-73.
- 43 33. Duplain H, Sartori C, Lepori M, et al. Exhaled nitric oxide in high-altitude pulmonary
44 edema: role in the regulation of pulmonary vascular tone and evidence for a role against
45 inflammation. *Am J Respir Crit Care Med.* 2000 Jul;162(1):221-4.

- 1 34. Swenson ER, Maggiorini M, Mongovin S, et al. Pathogenesis of high-altitude pulmonary
2 edema: inflammation is not an etiologic factor. *JAMA*. 2002;287:2228-2235.
- 3 35. Forward SA, Landowne M, Follansbee JN, et al. Effect of acetazolamide on acute
4 mountain sickness [Clinical Trial Controlled Clinical Trial]. *N Engl J Med*. 1968 Oct
5 17;279(16):839-45.
- 6 36. Swenson ER. Pharmacology of acute mountain sickness: old drugs and newer thinking
7 [Review]. *J Appl Physiol* (1985). 2016 Jan 15;120(2):204-15.
- 8 37. Swenson ER, Robertson HT, Hlastala MP. Effects of Carbonic-Anhydrase Inhibition on
9 Ventilation-Perfusion Matching in the Dog Lung. *J Clin Invest*. 1993 Aug;92(2):702-709.
- 10 38. Swenson ER. Carbonic anhydrase inhibitors and high altitude illnesses. *Subcell Biochem*.
11 2014;75:361-86.
- 12 39. Berg JT, Ramanathan S, Gabrielli MG, et al. Carbonic anhydrase in mammalian vascular
13 smooth muscle. *J Histochem Cytochem*. 2004 Aug;52(8):1101-6.
- 14 40. Teppema LJ, Balanos GM, Steinback CD, et al. Effects of acetazolamide on ventilatory,
15 cerebrovascular, and pulmonary vascular responses to hypoxia. *Am J Respir Crit Care Med*.
16 2007 Feb 1;175(3):277-81.
- 17 41. Fan JL, Burgess KR, Thomas KN, et al. Effects of acetazolamide on cerebrovascular
18 function and breathing stability at 5050 m. *J Physiol*. 2012;590(5):1213-1225.
- 19 42. Burgess KR, Lucas SJE, Shepherd K, et al. Influence of cerebral blood flow on central
20 sleep apnea at high altitude. *Sleep*. 2014;37(10):1679-1687.
- 21 43. Cain SM, Dunn JE, 2nd. Increase of arterial oxygen tension at altitude by carbonic
22 anhydrase inhibition. *J Appl Physiol*. 1965 Sep;20(5):882-4.
- 23 44. Birmingham Medical Research Expeditionary S. Acetazolamide in control of acute
24 mountain sickness. *Lancet*. 1981 Jan 24;1(8213):180-3.
- 25 45. Milles JJ, Chesner IM, Oldfield S, et al. Effect of acetazolamide on blood gases and 2,3
26 DPG during ascent and acclimatization to high altitude. *Postgrad Med J*. 1987 Mar;63(737):183-
27 4.
- 28 46. Ritchie ND, Baggott AV, Andrew Todd WT. Acetazolamide for the Prevention of Acute
29 Mountain Sickness — A Systematic Review and Meta-analysis. *Journal of Travel Medicine*.
30 2012 July 30;19(5):298-307.
- 31 47. Swenson ER, Leatham KL, Roach RC, et al. Renal carbonic anhydrase inhibition reduces
32 high altitude sleep periodic breathing. *Respir Physiol*. 1991 Dec;86(3):333-43.
- 33 48. Teppema L, Berkenbosch A, DeGoede J, et al. Carbonic anhydrase and control of
34 breathing: different effects of benzolamide and methazolamide in the anaesthetized cat. *J Physiol*.
35 1995 Nov 1;488 (Pt 3):767-77.
- 36 *49. Bradwell AR, Ashdown K, Rue C, et al. Acetazolamide reduces exercise capacity
37 following a 5-day ascent to 4559 m in a randomised study. *BMJ Open Sport Exerc Med*.
38 2018;4(1):e000302.
- 39 Most recent evidence provided supporting the earlier hypothesized need for individualized
40 acetazolamide dosing, particularly in older sojourners.
- 41 *50. Elisabeth E, Hannes G, Johannes B, et al. Effects of low-dose acetazolamide on exercise
42 performance in simulated altitude. *Int J Physiol Pathophysiol Pharmacol*. 2017;9(2):28-34.
- 43 Evidence supporting the foundation for previous speculation of adverse effects (reduced exercise
44 capacity) of acetazolamide, particularly in older subjects at high altitude.

- 1 51. Dominelli PB, McNeil CJ, Vermeulen TD, et al. Effect of acetazolamide and
2 methazolamide on diaphragm and dorsiflexor fatigue: a randomized controlled trial. *J Appl*
3 *Physiol* (1985). 2018 May 24.
- 4 52. Basnyat B, Gertsch JH, Holck PS, et al. Acetazolamide 125 mg BD is not significantly
5 different from 375 mg BD in the prevention of acute mountain sickness: The prophylactic
6 acetazolamide dosage comparison for efficacy (PACE) trial. *High altitude medicine & biology*.
7 2006 Spr;7(1):17-27.
- 8 53. Basnyat B, Gertsch JH, Johnson EW, et al. Efficacy of low-dose acetazolamide (125 mg
9 BID) for the prophylaxis of acute mountain sickness: A prospective, double-blind, randomized,
10 placebo-controlled trial. *High altitude medicine & biology*. 2003 Spr;4(1):45-52.
- 11 54. Ritchie ND, Baggott AV, Andrew Todd WT. Acetazolamide for the prevention of acute
12 mountain sickness--a systematic review and meta-analysis. *J Travel Med*. 2012 Sep-
13 Oct;19(5):298-307.
- 14 55. Low EV, Avery AJ, Gupta V, et al. Identifying the lowest effective dose of
15 acetazolamide for the prophylaxis of acute mountain sickness: systematic review and meta-
16 analysis. *BMJ*. 2012 Oct 18;345:e6779.
- 17 *56. Luks AM, McIntosh SE, Grissom CK, et al. Wilderness Medical Society Practice
18 Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2014 Update. *Wild*
19 *Environ Med*. 2014;25(4):S4-S14.
- 20 Most up to date Wilderness Medical Society guidelines highlighting existing prevention and
21 treatment strategies of acute altitude illnesses addressed herein.
- 22 57. Netzer N, Strohl K, Faulhaber M, et al. Hypoxia-Related Altitude Illnesses. *Journal of*
23 *Travel Medicine*. 2013 Jul;20(4):247-255.
- 24 58. Ritschel WA, Paulos C, Arancibia A, et al. Pharmacokinetics of acetazolamide in healthy
25 volunteers after short- and long-term exposure to high altitude. *J Clin Pharmacol*. 1998
26 Jun;38(6):533-539.
- 27 59. McIntosh S, Hemphill M, McDevitt M, et al. Reduced Acetazolamide Dosing for Acute
28 Mountain Sickness Prevention Study: A Comparison of 62.5 vs 125 mg BID (the RAD AMS
29 prevention study). *Wild Environ Med*. 2017;28(4):365-366.
- 30 *60. Bailey DM, Stacey BS, Gumbleton M. A Systematic Review and Meta-Analysis Reveals
31 Altered Drug Pharmacokinetics in Humans During Acute Exposure to Terrestrial High
32 Altitude—Clinical Justification for Dose Adjustment? *High Alt Med Biol*. 2018;0(0):1-8.
- 33 Exhaustive review regarding altered drug pharmacokinetics at high altitude and emphasizes the
34 need for dosage adjustments upon exposure to high altitude.
- 35 61. Bailey D. On the significance of altered drug pharmacokinetics-pharmacodynamics at
36 high altitude. *High altitude medicine & biology*. 2017;18:88-89.
- 37 **62. Wright A, Brearey S, Imray C. High hopes at high altitudes: pharmacotherapy for acute
38 mountain sickness and high-altitude cerebral and pulmonary oedema. *Expert Opin Pharmacol*.
39 2008 Jan;9(1):119-127.
- 40 The original expert opinion paper that the present paper aimed to review and build upon to
41 include more recent findings and updates concerning pathophysiology, prevention, and treatment
42 of high altitude illnesses.
- 43 63. Wright AD, Bradwell AR, Fletcher RF. Methazolamide and acetazolamide in acute
44 mountain sickness [Clinical Trial Comparative Study Controlled Clinical Trial Research Support,
45 Non-U.S. Gov't]. *Aviat Space Environ Med*. 1983 Jul;54(7):619-21.

- 1 64. Teppema LJ, Bijl H, Gourabi BM, et al. The carbonic anhydrase inhibitors
2 methazolamide and acetazolamide have different effects on the hypoxic ventilatory response in
3 the anaesthetized cat. *J Physiol-London*. 2006 Jul 15;574(2):565-572.
- 4 **65. Lisk C, McCord J, Bose S, et al. Nrf-2 activation: a potential strategy for the prevention
5 of acute mountain sickness. *Free Radical Biology & Medicine*. 2013;63:264-273. Validated
6 evidence in support for Nrf-2 as a novel pharmacotherapeutic option at altitude.
- 7 66. Strapazzon G, Malacrida S, Vezzoli A, et al. Oxidative stress response to acute hypobaric
8 hypoxia and its association with indirect measurement of increased intracranial pressure: a field
9 study. *Sci Rep-Uk*. 2016 Aug 31;6.
- 10 67. Collier DJ, Wolff CB, Hedges AM, et al. Benzolamide improves oxygenation and
11 reduces acute mountain sickness during a high-altitude trek and has fewer side effects than
12 acetazolamide at sea level. *Pharmacol Res Perspect*. 2016 Jun;4(3):e00203.
- 13 68. Collier DJ, Wolff CB, Hedges AM, et al. Benzolamide improves oxygenation and
14 reduces acute mountain sickness during a high-altitude trek and has fewer side effects than
15 acetazolamide at sea level. *Pharmacol Res Perspe*. 2016 Jun;4(3).
- 16 69. Kronenberg RS, Cain SM. Effects of Acetazolamide and Hypoxia on Cerebrospinal Fluid
17 Bicarbonate. *Journal of Applied Physiology*. 1968;24(1):17-+.
- 18 70. Hackett PH, Roach RC. High altitude cerebral edema [Review]. *High altitude medicine
19 & biology*. 2004 Summer;5(2):136-46
- 20 71. Chen GZ, Zheng CR, Qin J, et al. Inhaled Budesonide Prevents Acute Mountain Sickness
21 in Young Chinese Men. *J Emerg Med*. 2015 Feb;48(2):197-206.
- 22 72. Berger MM, Macholz F, Schmidt P, et al. Inhaled Budesonide Does Not Affect Hypoxic
23 Pulmonary Vasoconstriction at 4559 Meter of Altitude. *High altitude medicine & biology*. 2018
24 Jan 3.
- 25 73. Lipman GS, Pomeranz D, Burns P, et al. Budesonide Versus Acetazolamide for
26 Prevention of Acute Mountain Sickness. *The American journal of medicine*. 2018
27 Feb;131(2):200 e9-200 e16.
- 28 74. Naeije R, Swenson ER. Inhaled budesonide for acute mountain sickness. *Eur Respir J*.
29 2018 Sep 1;50(3).
- 30 75. Loepky JA, Roach RC, Selland MA, et al. Body-Fluid Alterations during Head-down
31 Bed Rest in Men at Moderate Altitude. *Aviat Space Envir Md*. 1993 Apr;64(4):265-274.
- 32 76. Hackett PH, Rennie D, Hofmeister SE, et al. Fluid Retention and Relative
33 Hypoventilation in Acute Mountain-Sickness. *Respiration*. 1982;43(5):321-329.
- 34 77. Schoene RB, Hackett PH, Henderson WR, et al. High-Altitude Pulmonary-Edema -
35 Characteristics of Lung Lavage Fluid. *Jama-J Am Med Assoc*. 1986 Jul 4;256(1):63-69.
- 36 78. Hackett PH, Roach RC, Schoene RB, et al. Abnormal Control of Ventilation in High-
37 Altitude Pulmonary-Edema. *Journal of Applied Physiology*. 1988 Mar;64(3):1268-1272.
- 38 79. Matsuzawa Y, Fujimoto K, Kobayashi T, et al. Blunted hypoxic ventilatory drive in
39 subjects susceptible to high-altitude pulmonary edema. *J Appl Physiol* (1985). 1989
40 Mar;66(3):1152-7.
- 41 80. Schoene RB. Illnesses at high altitude. *Chest*. 2008 Aug;134(2):402-416
- 42 81. Swenson ER, Duncan TB, Goldberg SV, et al. Diuretic effect of acute hypoxia in humans:
43 relationship to hypoxic ventilatory responsiveness and renal hormones. *J Appl Physiol* (1985).
44 1995 Feb;78(2):377-83.
- 45 82. Gatterer H, Wille M, Faulhaber M, et al. Association between body water status and
46 acute mountain sickness. *PLoS One*. 2013;8(8).

- 1 83. Basnyat B, Holck PS, Pun M, et al. Spironolactone does not prevent acute mountain
2 sickness: a prospective, double-blind, randomized, placebo-controlled trial by SPACE Trial
3 Group (spironolactone and acetazolamide trial in the prevention of acute mountain sickness
4 group). *Wilderness & Environmental Medicine*. 2011;22(1):15-22.
- 5 84. Woods DR, Montgomery HE. Angiotensin-Converting Enzyme and Genetics at High
6 Altitude. *High Alt Med Biol*. 2001;2(2):201-210.
- 7 85. Kumar R, Qadar Pasha MA, Khan AP, et al. Association of high-altitude systemic
8 hypertension with the deletion allele-of the angiotensin-converting enzyme (ACE) gene.
9 *International journal of biometeorology*. 2003 Sep;48(1):10-4.
- 10 86. Swenson ER. Ace inhibitors and high altitude. *High altitude medicine & biology*. 2004
11 Spr;5(1):92-94.
- 12 *87. Wang YX, Lu HX, Chen Y, et al. The association of angiotensin-converting enzyme gene
13 insertion/deletion polymorphisms with adaptation to high altitude: A meta-analysis. *Journal of
14 the Renin-Angiotensin-Aldosterone System*. 2016 Jan-Mar;17(1).
15 Contributes information that will help the development of an individualized and genetic profiling
16 based approach to the prevention and treatment of altitude illnesses.
- 17 88. Bartsch P, Maggiorini M, Ritter M, et al. Prevention of high-altitude pulmonary edema
18 by nifedipine [Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't]. *N
19 Engl J Med*. 1991 Oct 31;325(18):1284-9.
- 20 89. Cargill RI, Lipworth BJ. Lisinopril attenuates acute hypoxic pulmonary vasoconstriction
21 in humans. *Chest*. 1996 Feb;109(2):424-429.
- 22 90. Parati G, Agostoni P, Basnyat B, et al. Clinical recommendations for high altitude
23 exposure of individuals with pre-existing cardiovascular conditions: A joint statement by the
24 European Society of Cardiology, the Council on Hypertension of the European Society of
25 Cardiology, the European Society of Hypertension, the International Society of Mountain
26 Medicine, the Italian Society of Hypertension and the Italian Society of Mountain Medicine. *Eur
27 Heart J*. 2018 May 1;39(17):1546-1554.
- 28 91. Pialoux V, Foster GE, Ahmed SB, et al. Losartan abolishes oxidative stress induced by
29 intermittent hypoxia in humans [Randomized Controlled Trial Research Support, Non-U.S.
30 Gov't]. *J Physiol*. 2011 Nov 15;589(Pt 22):5529-37.
- 31 92. Chandel S, Doza B, Bigvijay K. Association of High Altitude Hypertension with
32 Angiotensin Converting Enzyme (ACE) Gene Insertion/Deletion Polymorphism. *Urology &
33 Nephrology*. 2017;5(1):1-7.
- 34 93. Parati G, Agostoni P, Basnyat B, et al. Clinical recommendations for high altitude
35 exposure of individuals with pre-existing cardiovascular conditions. *Eur Heart J*. 2018 Jan 11.
- 36 94. Bilo G, Villafuerte FC, Faini A, et al. Ambulatory Blood Pressure in Untreated and
37 Treated Hypertensive Patients at High Altitude The High Altitude Cardiovascular Research-
38 Andes Study. *Hypertension*. 2015 Jun;65(6):1266-U199.
- 39 95. Parati G, Bilo G, Faini A, et al. Changes in 24 h ambulatory blood pressure and effects of
40 angiotensin II receptor blockade during acute and prolonged high-altitude exposure: a
41 randomized clinical trial. *Eur Heart J*. 2014 Nov 21;35(44):3113-22.
- 42 96. Chen CH, Chen ACH, Liu HJ. Involvement of nitric oxide and N-methyl-D-aspartate in
43 acute hypoxic altitude convulsion in mice. *Aviat Space Envir Md*. 1997 Apr;68(4):296-299.
- 44 97. Xie JH, Lu GW, Hou YZ. Role of excitatory amino acids in hypoxic preconditioning.
45 *Biol Signal Recept*. 1999 Jul-Oct;8(4-5):267-274.

- 1 98. Dumont L, Lysakowski C, Tramer MR, et al. Magnesium for the prevention and
2 treatment of acute mountain sickness. *Clin Sci*. 2004 Mar;106(3):269-277.
- 3 99. Lysakowski C, Von Elm E, Dumont L, et al. Effect of magnesium, high altitude and
4 acute mountain sickness on blood flow velocity in the middle cerebral artery. *Clin Sci*. 2004
5 Mar;106(3):279-285.
- 6 100. Gertsch JH, Lipman GS, Holck PS, et al. Prospective, Double-Blind, Randomized,
7 Placebo-Controlled Comparison of Acetazolamide Versus Ibuprofen for Prophylaxis Against
8 High Altitude Headache: The Headache Evaluation at Altitude Trial (HEAT). *Wild Environ Med*.
9 2010 Fal;21(3):236-243.
- 10 101. Gertsch JH, Corbett B, Holck PS, et al. Altitude Sickness in Climbers and Efficacy of
11 NSAIDs Trial (ASCENT): Randomized, Controlled Trial of Ibuprofen Versus Placebo for
12 Prevention of Altitude Illness. *Wild Environ Med*. 2012 Win;23(4):307-315.
- 13 102. Lipman GS, Kanaan NC. Ibuprofen Prevents Altitude Illness: A Randomized Controlled
14 Trial for Prevention of Altitude Illness With Nonsteroidal Anti-inflammatories (vol 23, pg 293,
15 2012). *Wild Environ Med*. 2012 Win;23(4):383-383.
- 16 103. Harris NS, Wenzel RP, Thomas SH. High altitude headache: efficacy of acetaminophen
17 vs. ibuprofen in a randomized, controlled trial. *J Emerg Med*. 2003 May;24(4):383-7.
- 18 104. Kanaan NC, Peterson AL, Holck PS, et al. Prophylactic Acetaminophen or Ibuprofen
19 Results in Equivalent Acute Mountain Sickness Incidence at High Altitude: A Prospective
20 Randomized Trial. *Wilderness Environ Med*. 2017;28(2):72-78.
- 21 105. Droma Y, Hanaoka M, Ota M, et al. Positive association of the endothelial nitric oxide
22 synthase gene polymorphisms with high-altitude pulmonary edema. *Circulation*. 2002 Aug
23 13;106(7):826-830.
- 24 106. Wright A, Brearey S, Imray C. High hopes at high altitudes: pharmacotherapy for acute
25 mountain sickness and high-altitude cerebral and pulmonary oedema. *Expert Opin Pharmacother*.
26 2008 Jan;9(1):119-27.
- 27 107. Donnelly J, Cowan DC, Yeoman DJ, et al. Exhaled nitric oxide and pulmonary artery
28 pressures during graded ascent to high altitude. *Respir Physiol Neurobiol*. 2011 Aug
29 15;177(3):213-7.
- 30 108. Wang P, Ha AYN, Kidd KK, et al. A Variant of the Endothelial Nitric Oxide Synthase
31 Gene (NOS3) Associated with AMS Susceptibility Is Less Common in the Quechua, a High
32 Altitude Native Population. *High altitude medicine & biology*. 2010 Apr;11(1):27-30.
- 33 109. Luo Y, Chen Y, Zhang Y, et al. Association of endothelial nitric oxide synthase (eNOS)
34 G894T polymorphism with high altitude pulmonary edema susceptibility: a meta-analysis.
35 *Wilderness Environ Med*. 2012 Sep;23(3):270-4.
- 36 110. Rossetti GMK, Macdonald JH, Wylie LJ, et al. Dietary nitrate supplementation increases
37 acute mountain sickness severity and sense of effort during hypoxic exercise. *J Appl Physiol*
38 (1985). 2017 Oct 1;123(4):983-992.
- 39 111. Hoschele S, Marirbaurl H. Alveolar flooding at high altitude: Failure of reabsorption?
40 *News Physiol Sci*. 2003;18(Apr):55-59.
- 41 112. West JB, Tsukimoto K, Mathieucostello O, et al. Stress Failure in Pulmonary Capillaries.
42 *Journal of Applied Physiology*. 1991 Apr;70(4):1731-1742.
- 43 113. Paralikar SJ, Paralikar JH. High-altitude medicine. *Indian journal of occupational and*
44 *environmental medicine*. 2010 Jan;14(1):6-12.
- 45 114. Oelz O, Maggiorini M, Ritter M, et al. Nifedipine for high altitude pulmonary oedema
46 [Research Support, Non-U.S. Gov't]. *Lancet*. 1989 Nov 25;2(8674):1241-4.

- 1 115. Xu Y, Liu Y, Liu J, et al. Meta-Analysis of Clinical Efficacy of Sildenafil, a
2 Phosphodiesterase Type-5 Inhibitor on High Altitude Hypoxia and Its Complications. *High*
3 *altitude medicine & biology*. 2014;15(1):46-51.
- 4 116. Wang JF, Zhang Q, Chen MD, et al. First Chemical Characterization of Refractory Black
5 Carbon Aerosols and Associated Coatings over the Tibetan Plateau (4730 m a.s.l). *Environ Sci*
6 *Technol*. 2017 Dec 19;51(24):14072-14082.
- 7 117. Shah NM, Hussain S, Cooke M, et al. Wilderness medicine at high altitude: recent
8 developments in the field. *Open Access J Sports*. 2015;6:319-328.
- 9 118. Maggiorini M., Brunner-La Rocca H.P., Peth S., et al. Both tadalafil and dexamethasone
10 may reduce the incidence of high-altitude pulmonary edema: a randomized trial. *Ann Intern Med*.
11 2006;145(7):498-506.
- 12 119. Leshem E, Caine Y, Rosenberg E, et al. Tadalafil and acetazolamide versus
13 acetazolamide for the prevention of severe high-altitude illness. *J Travel Med*. 2012 Sep-
14 Oct;19(5):308-10.
- 15 120. Chan CW, Hoar H, Pattinson K, et al. Effect of sildenafil and acclimatization on cerebral
16 oxygenation at altitude. *Clin Sci (Lond)*. 2005;109(3):119-124.
- 17 121. Roach RC, Bärtsch PH, Hackett PH, et al. The Lake Louise Acute Mountain Sickness
18 Scoring System. *Hypoxia and Molecular Medicine*. 1993:272-274.
- 19 122. Van Osta A, Moraine JJ, Melot C, et al. Effects of high altitude exposure on cerebral
20 hemodynamics in normal subjects. *Stroke*. 2005 Mar;36(3):557-560.
- 21 123. Swenson ER. Carbonic anhydrase inhibitors and hypoxic pulmonary vasoconstriction.
22 *Respir Physiol Neurobiol*. 2006 Apr 28;151(2-3):209-16.
- 23 124. Maggiorini M. High altitude-induced pulmonary oedema [Review]. *Cardiovascular*
24 *research*. 2006 Oct 1;72(1):41-50.
- 25 125. Sikri G. Role of dexamethasone in prevention of high altitude pulmonary edema
26 [Comment Letter]. *Journal of occupational health*. 2015;57(2):200.
- 27 126. Jones BE, Stokes S, McKenzie S, et al. Management of HAPE in the Himalaya: a review
28 of 56 cases presenting at Pheriche Medical Aid Post (4240m). *Wilderness & Environmental*
29 *Medicine*. 2013;24(1):32-36.
- 30 127. Frise MC, Robbins PA. Iron, oxygen, and the pulmonary circulation. *Journal of Applied*
31 *Physiology*. 2015 Dec 15;119(12):1421-1431.
- 32 128. Ren XW, Zhang QY, Wang H, et al. Effect of Intravenous Iron Supplementation on
33 Acute Mountain Sickness: A Preliminary Randomized Controlled Study. *Med Sci Monitor*. 2015
34 Jul 15;21.
- 35 129. Geldart A, Vitali S, Touma M, et al. The effect of acidosis on pulmonary vascular smooth
36 muscle cell metabolic response to hypoxia: implications for Pulmonary Hypertension. *Faseb J*.
37 2011 Apr;25.
- 38 130. Eddahibi S, Raffestin B, Clozel M, et al. Protection from Pulmonary-Hypertension with
39 an Orally-Active Endothelin Receptor Antagonist in Hypoxic Rats. *Am J Physiol-Heart C*. 1995
40 Feb;268(2):H828-H835.
- 41 131. DiCarlo VS, Chen SJ, Meng QC, et al. ETA-receptor antagonist prevents and reverses
42 chronic hypoxia-induced pulmonary hypertension in rat [Research Support, Non-U.S. Gov't
43 Research Support, U.S. Gov't, P.H.S.]. *Am J Physiol*. 1995 Nov;269(5 Pt 1):L690-7.
- 44 132. Chen SJ, Chen YF, Meng QC, et al. Endothelin-receptor antagonist bosentan prevents
45 and reverses hypoxic pulmonary hypertension in rats. *J Appl Physiol (1985)*. 1995
46 Dec;79(6):2122-31.

- 1 133. Franco-Cereceda A, Holm P. Selective or nonselective endothelin antagonists in porcine
2 hypoxic pulmonary hypertension? [Research Support, Non-U.S. Gov't]. *Journal of*
3 *cardiovascular pharmacology*. 1998;31 Suppl 1:S447-52.
- 4 134. Naeije R, Huez S, Lamotte M, et al. Pulmonary artery pressure limits exercise capacity at
5 high altitude. *Eur Respir J*. 2010 Nov;36(5):1049-1055.
- 6 135. Elshaboury SM, Anderson JR. Ambrisentan for the treatment of pulmonary arterial
7 hypertension: improving outcomes. *Patient Prefer Adher*. 2013;7:401-409.
- 8 136. Ferguson S, Loomis Z, Harral J, et al. Therapeutic Role of Ambrisentan for the Treatment
9 of Hypoxic Pulmonary Vasoconstriction: Impact of Intrapulmonary Delivery. *Faseb J*. 2016
10 Apr;30.
- 11 137. Ghofrani HA, Voswinckel R, Reichenberger F, et al. Hypoxia- and non-hypoxia-related
12 pulmonary hypertension - established and new therapies [Review]. *Cardiovasc Res*. 2006 Oct
13 1;72(1):30-40.
- 14 138. Pham I, Wuerzner G, Richalet JP, et al. Bosentan effects in hypoxic pulmonary
15 vasoconstriction: Preliminary study in subjects with or without high altitude pulmonary edema-
16 history. *Pulmonary Circulation*. 2012;2(1):28-33.
- 17 139. Kojonazarov B, Isakova J, Imanov B, et al. Bosentan reduces pulmonary artery pressure
18 in high altitude residents. *High Alt Med Biol*. 2012 Sep;13(3):217-23.
- 19 140. Hackett PH, Rennie D, Grover RF, et al. Acute mountain sickness and the edemas of high
20 altitude: a common pathogenesis? *Respir Physiol*. 1981 Dec;46(3):383-90.
- 21 141. Modesti PA, Vanni S, Morabito M, et al. Role of endothelin-1 in exposure to high
22 altitude: Acute Mountain Sickness and Endothelin-1 (ACME-1) study. *Circulation*. 2006 Sep
23 26;114(13):1410-6.
- 24 142. Selej M, Romero AJ, Channick RN, et al. Development of macitentan for the treatment of
25 pulmonary arterial hypertension. *Ann Ny Acad Sci*. 2015;1358:68-81.
- 26 143. Betge S, Jung C, Franz M. Influence of macitentan on the vascular tone and recruitment
27 of capillaries under hypobaric hypoxia in high altitude. *European Heart Journal*. 2017;38(1).
- 28 144. Jansa P, Pulido T. Macitentan in Pulmonary Arterial Hypertension: A Focus on
29 Combination Therapy in the SERAPHIN Trial. *Am J Cardiovasc Drug*. 2018 Feb;18(1):1-11.
- 30 **145. Liu B, Chen J, Zhang L, et al. IL-10 Dysregulation in Acute Mountain Sickness Revealed
31 by Transcriptome Analysis. *Front Immunol*. 2017 May 30;8.
- 32 Evaluation of the involvement of the inflammatory responses to hypoxia and the associated
33 involvement of IL-10 providing sufficient evidence in support for the incorporation of IL-10
34 upregulators in the prevention and treatment of altitude illnesses.
- 35 146. Boos CJ, Woods DR, Varias A, et al. High Altitude and Acute Mountain Sickness and
36 Changes in Circulating Endothelin-1, Interleukin-6, and Interleukin-17a. *High altitude medicine*
37 *& biology*. 2016;17(1):25-31.
- 38 147. Julian CG, Subudhi AW, Wilson MJ, et al. Acute mountain sickness, inflammation, and
39 permeability: new insights from a blood biomarker study. *Journal of Applied Physiology*. 2011
40 Aug;111(2):392-399.
- 41 *148. Boos CJ, Woods DR, Varias A, et al. High Altitude and Acute Mountain Sickness and
42 Changes in Circulating Endothelin-1, Interleukin-6, and Interleukin-17a. *High Alt Med Biol*.
43 2016 Mar;17(1):25-31.
- 44 Recent evidence to support the involvement of humoral factors involved in the inflammatory
45 response to hypoxia.

- 1 149. Jafarian S, Abolfazli R, Gorouhi F, et al. Gabapentin for prevention of hypobaric
2 hypoxia-induced headache: randomized double-blind clinical trial [Randomized Controlled Trial
3 Research Support, Non-U.S. Gov't]. *Journal of neurology, neurosurgery, and psychiatry*. 2008
4 Mar;79(3):321-3.
- 5 150. Jafarian S, Gorouhi F, Salimi S, et al. Low-dose gabapentin in treatment of high-altitude
6 headache [Randomized Controlled Trial]. *Cephalalgia : an international journal of headache*.
7 2007 Nov;27(11):1274-7.
- 8 151. Seupaul RA, Welch JL, Malka ST, et al. Pharmacologic Prophylaxis for Acute Mountain
9 Sickness: A Systematic Shortcut Review. *Annals of Emergency Medicine*. 2012 Apr;59(4):307-
10 317.
- 11 152. Grimminger J, Richter M, Tello K, et al. Thin Air Resulting in High Pressure: Mountain
12 Sickness and Hypoxia-Induced Pulmonary Hypertension. *Can Respir J*. 2017.
- 13 153. Kojonazarov B, Myrzaakhmatova A, Sooronbaev T, et al. Effects of fasudil in patients
14 with high-altitude pulmonary hypertension [Clinical Trial Letter Research Support, Non-U.S.
15 Gov't]. *Eur Respir J*. 2012 Feb;39(2):496-8.
- 16 154. Kushiyama T, Oda T, Yamamoto K, et al. Protective effects of Rho kinase inhibitor
17 fasudil on rats with chronic kidney disease [Comparative Study]. *American journal of
18 physiology Renal physiology*. 2013 Jun 1;304(11):F1325-34.
- 19 155. Krause LK. Gene Expression Patterns in Patients with High-Altitude Pulmonary Edema:
20 A Gene Microarray Analysis. *Yale Medicine Thesis Digital Library: Yale Univeristy*; 2007.
- 21 *156. Andrews J, Martina S, Natoli M, et al. The Effect of Riociguat on Gas Exchange,
22 Exercise Performance, and Pulmonary Artery Pressure During Acute Altitude Exposure. *Wild
23 Environ Med*. 2016;27(3):428.
- 24 Recent works providing concrete evidence supporting the use of Riociguat at altitude.
- 25 157. Hall FG. The effect of altitude on the affinity of hemoglobin for oxygen. *J Biol Chem*.
26 1936 Sep;115(2):485-490.
- 27 158. Geng X, Dufu K, Hutchaleelaha A, et al. Increased hemoglobin-oxygen affinity
28 ameliorates bleomycin-induced hypoxemia and pulmonary fibrosis. *Physiol Rep*. 2016 Sep;4(17).
- 29 159. Dufu K, Lehrer-Graiwer J, Ramos E, et al. GBT440 inhibits sickling of sickle cell trait
30 blood under in vitro conditions mimicking strenuous exercise. *Hematol Rep*. 2016;8(3):37-41.
- 31 160. Chen XQ, Kong FP, Zhao Y, et al. High-altitude hypoxia induces disorders of the brain-
32 endocrine-immune network through activation of corticotropin-releasing factor and its type-1
33 receptors. *Chinese Journal of Physiology*. 2012;28(6):481-487.
- 34 *161. Hao K, Kong FP, Gao YQ, et al. Inactivation of corticotropin-releasing hormone-induced
35 insulinotropic role by high-altitude hypoxia. *Diabetes*. 2015 Mar;64(3):785-95.
- 36 Concrete evidence of change in corticotropin-releasing hormone associated with altitude and,
37 thus, providing a foundation for the argument made herein.
- 38 162. Song TT, Bi YH, Gao YQ, et al. Systemic pro-inflammatory response facilitates the
39 development of cerebral edema during short hypoxia. *J Neuroinflammation*. 2016 Mar
40 11;13(1):63.
- 41 163. Hu SL, Shi JT, Xiong W, et al. Oxiracetam or fastigial nucleus stimulation reduces
42 cognitive injury at high altitude. *Brain Behav*. 2017 Oct;7(10).
- 43 164. MacInnis MJ, Wang P, Koehle MS, et al. The genetics of altitude tolerance: the evidence
44 for inherited susceptibility to acute mountain sickness. *J Occup Environ Med*. 2011
45 Feb;53(2):159-68.

- 1 165. Jiang CZ, Li FZ, He MA, et al. [Glutathione S-transferase M1, T1 genotypes and the risk
2 of mountain sickness]. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*. 2005
3 Jun;23(3):188-90.
- 4 166. Jiang CZ, Li FZ, Sun SY, et al. [The unbalance of anti-oxidation enzyme system and
5 lipid peroxidation in acute high altitude sickness]. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing
6 Za Zhi*. 2004 Apr;22(2):138-9.
- 7 167. Fiander H, Schneider H. Dietary ortho phenols that induce glutathione S-transferase and
8 increase the resistance of cells to hydrogen peroxide are potential cancer chemopreventives that
9 act by two mechanisms: the alleviation of oxidative stress and the detoxification of mutagenic
10 xenobiotics. *Cancer Letters*. 2000;156(2):117 - 124.
- 11 168. Fiander H, Schneider H. Compounds that induce isoforms of glutathione S-transferase
12 with properties of a critical enzyme in defense against oxidative stress. *Biochem Biophys Res
13 Commun*. 1999 Sep 7;262(2):591-595.
- 14 169. Singh M, Tulsawani R, Koganti P, et al. *Cordyceps sinensis* increases hypoxia tolerance
15 by inducing heme oxygenase-1 and metallothionein via Nrf2 activation in human lung epithelial
16 cells. *Biomed Res Int*. 2013;2013:569206.
17
18