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Chapter

Sleep Disorder at High Altitude

Fanyi Kong

Abstract

In this chapter, we discuss the occurrence, mechanism, clinical manifestations, outcomes, and managements of a commonly encountered sleep disorder of someone traveling in high altitude for working and sight-seeing. Humans ascending to altitudes above 2500 m usually suffer from substantial disturbances in sleep quality as difficulty in sleep onset, frequent awakenings, respiratory disturbance, and a feeling of drowsiness on the next day. Data obtained from polysomnographic studies demonstrated several variations of sleep architecture in those healthy subjects ascending to high altitude during sleep, including periodic breathing and decreased non-rapid eye movement deep sleep stage 3 and 4 (in new nomenclature N3), which were usually accompanied by and the lowered arterial O_2 and restricted ventilation. Hypoxia is most severe during sleep and in correspondence to periodic breathing and sleep disturbance at high altitude. Poor sleep quality impairs cognition and executive abilities at high altitude though it may largely be improved after full time of acclimatization. Evidence-based choices for clinicians to treat sleep disorder at high altitude are relatively scarce at present. Supplemental oxygen and dietary nitrate are effective in alleviating nocturnal hypoxia. There is strong evidence supporting the efficacy and safety of acetazolamide and nonbenzodiazepines in minimizing periodic breathing and improving sleep quality at high altitude.

Keywords: sleep architecture, sleep disorder, sleep quality, periodic breathing, high altitude, treatment

1. Introduction

Every year, thousands of people come from the lowlands to high altitude such as the Qinghai-Tibetan plateau, the Andes, and the Alps, for sight-seeing and mountaineering. Although identification on high altitude is controversial [1, 2] (see **Table 1**), altitude illnesses do not generally occur until 2500 m altitude or greater [2]. Currently, there are hundreds of thousands of non-native people working and living in these areas at altitudes ranging from 4000 to 5072 m including mountaineers, search and rescue personnel, and military personnel.

Poor sleep quality is a common experience for new arrivals at high altitude in the days to weeks following acute ascent. They often encounter with increased awakenings, frequent brief arousals, a sense of suffocation relieved by a few deep breaths, and resumption of sleep, which is now known as periodic breathing (PB). Upon arising from sleep, the impression is one of greatly restless sleep. Poor sleep quality at high altitude is one of the serious complaints in people with mountain sickness and influences physical and mental well-being, which can manifest as impaired cognitive abilities [3, 4] and poor daytime performance [5]. Up to now,

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	Davis et al. [1]	Rolan [2]
High altitude	Beyond 2400 m	2500 m–3500 m
Very high altitude	Beyond 4000 m	3500 m–5800 m
Extremely high altitude	Beyond 5500 m	Beyond 5800 m

Table 1.
Identification of high altitude.

there are no acceptable diagnostic criteria for sleep disorder at high altitude. It is recognized as a symptom of mountain sickness rather than an altitude disease.

Here we discuss the features of sleep at high altitude with focus on the role and causes of PB in altitude sleep disturbance, subjective changes in sleep quality, objective variations in sleep architecture, and management of sleep disorder at high altitude. We also discuss whether it is appropriate to name it high-altitude sleep disorder (HASD) as one of the altitude-related illness in accordance with the nomenclature of other high-altitude diseases.

2. Breathing disturbance during sleep at high altitude

One of the most important characteristics of sleep disorder at high altitude is PB, which usually occurs at altitudes above 2000 m [6]. PB during sleep was first recorded in 1886 by Mosso [7] and further observed by Douglas and Haldane in 1909 [8]. It is considered that under high altitude hypoxic circumstances, breathing was stimulated by hypoxia, leading to hypocapnia and lessening of hypoxia, which triggers apnea during sleep. Apnea, in turn, restores ventilatory by raising PCO_2 and increasing hypoxia, generating the periodic respiratory cycle. This cyclical crescendo-decrescendo pattern periodicity usually consists of 2–4 breaths, separated by an apnea of 5–15 s in duration from the next burst of 2–4 breaths. Therefore, unstable breathing is the main characteristic of PB.

The extent of PB increased progressively as the altitude increased [9]. There is a strong positive correlation between PB and severity of acute mountain sickness (AMS) as assessed by Lake Louise (LL) score. With the increasing of altitude, normal values for partial pressure of arterial (PaO_2) decreased compared to sea level, pH changing to respiratory alkalosis with concomitant hypocapnia [10]. Above 4000 m altitude, PB exists in most people, but this phenomenon may be beneficial, because with the worsening of PB, a higher arterial oxygen saturation (SaO_2) was observed during sleep [10, 11]. After 3 months of acclimatization at 3800 altitude, PB could also be observed in lowlanders. Although acclimatized lowlanders experienced PB more frequently than native Tibetans at 89–85% of SaO_2 stage, there is no significant difference in total PB events occurring either in non-rapid eye movement (NREM) or rapid eye movement (REM) stage [12]. See details in **Figure 1**, periodic breathing during sleep between native Tibetans and acclimatized Han lowlanders at 3800 m altitude. Even for a longer time (13 months) of camp in the Antarctic base Concordia (3800 m), PB prevailed for the major part of sleeping time [13]. These findings from a cross-sectional and a longitudinal study support our current understanding which assumes PB would not be largely relieved after acclimatization.

The mechanism underlying this respiratory pattern for apnea and PB during sleep in hypoxic environments is believed to be a reduction in the PaO_2 and acid-base adjustments. The procedure of PB may be summarized as conflicting dynamics between hypoxic stimulation of ventilation and suppression of respiratory output

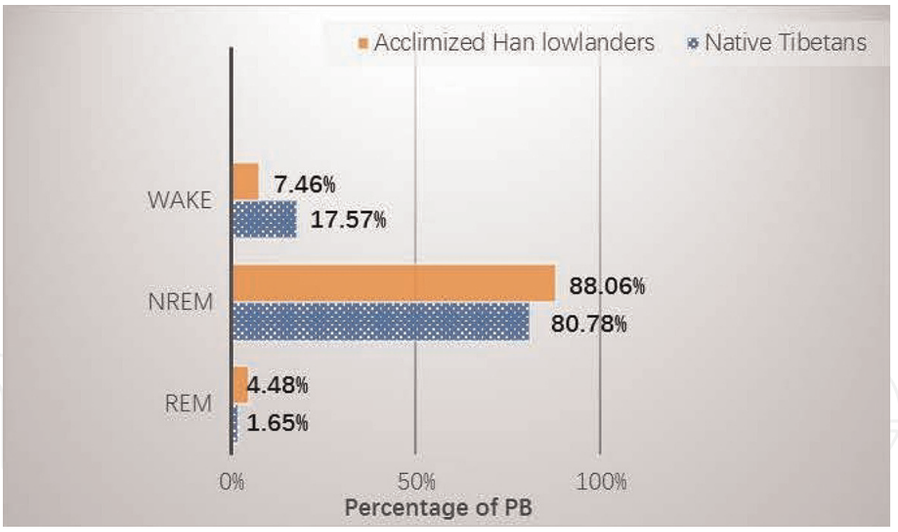


Figure 1.
Periodic breathing during sleep between native Tibetans and acclimatized Han lowlanders at 3800 altitude. Modified from Kong et al. [12].

from ensuing hypocapnia. These changes lead to alterations in chemoreflex control and cerebrovascular responses to changes in arterial O_2 which finally result in hyperventilation. For lowlanders, acclimatization to high altitude magnifies these changes. Briefly, an elevated chemosensitivity causes a more vigorous response to the rise in $PaCO_2$ while the apnea outweighs the improvements in the effectiveness of ventilation in changing the arterial O_2 caused by the chronic hypocapnia leading to the occurrence of PB [14].

The severity of PB is determined to be aggravated by an increasing neural respiratory drive (NRD), which can be measured by the electromyogram of the diaphragm. A sleep study in four healthy mountaineers performed at 3380, 4370, and 5570 m in the Andes, Argentina, confirmed this hypothesis [15]. A high NRD at altitude leads to a higher ventilation to maintain oxygenation, which results in more significant hypocapnia. This triggers apneas and O_2 desaturations, as indicated by the positive correlation between the EMG of the diaphragm and the O_2 desaturation index.

PB is considered to contribute to and/or be a result of sleep fragmentation by frequent arousals which may be responsible for poor sleep quality following altitude ascent. Sleep and arousals lead to greater breathing instability. Apnea is in correspondence to an increase in $PaCO_2$ and decrease in PaO_2 and consequently unstable ventilation. These changes in blood gases also lead to marked alterations in cerebral blood flow (CBF) which, in turn, may result in a sudden elevation (with reduced CBF) or reduction (with increased CBF) in brain stem pH.

Therefore, the uncomfortable sensation of sleep at high altitude is largely due to respiratory disturbance arising from the physiologic ventilatory dilemma of acute ascent, where stimulation by hypoxia alternates with inhibition by hypocapnic alkalosis.

3. Poor subjective sleep quality at high altitude

3.1 Evaluation and prevalence of poor sleep quality at high altitude

Subjective sleep quality at high altitude is usually evaluated by a questionnaire, e.g., sleep log questions, Pittsburgh Sleep Quality Index (PSQI), and Athens Insomnia Score (AIS). The prevalence of sleep disorder may differ considerably at altitude

from observational studies. At a 3500 m hotel, 46% of 100 Iranian ski tourists reported frequent awakenings and other subjective sleep disturbances [16]. At an altitude of 3700 m in Lhasa, Tibet, 36.8% of 180 Chinese stationed soldiers reported poor sleep quality as measured by PSQI [17]. Data analysis from the same sample also indicated that poor sleepers (defined as PSQI > 5) were 1.45 times greater in those with polycythemia than those without polycythemia [95% (confidence interval) CI 1.82–2.56] [4]. Report from early pharmacologic treatment trials in acute mountain sickness (AMS) suggested that 53–71% of participants reported difficulty sleeping [18, 19]. Of note, despite the 3 months of acclimatization, a greater proportion of poor sleepers were still observed in lowlanders stationed at 3800 altitude than the native Tibetans (90.91 vs. 45.45%, P = 0.004) [12].

3.2 Sleep quality and severity of mountain sickness

Poor sleep quality at high altitude was one of the most frequently reported symptoms in mountain sickness as assessed by the Lake Louise Symptom Questionnaire and the Qinghai Chronis Mountain Score [12], which are used to diagnose AMS [20] and evaluate severity of chronic mountain sickness(CMS) [21], respectively. This was confirmed by a study using PSQI and AIS which reports decreased subjective sleep quality at high altitude, especially reduced general sleep quality and prolonged sleep induction [22]. For workers rapidly transported from sea level to high altitude, there are no statistically significant differences in polysomnographic parameters between subjects with AMS and those without AMS [23].

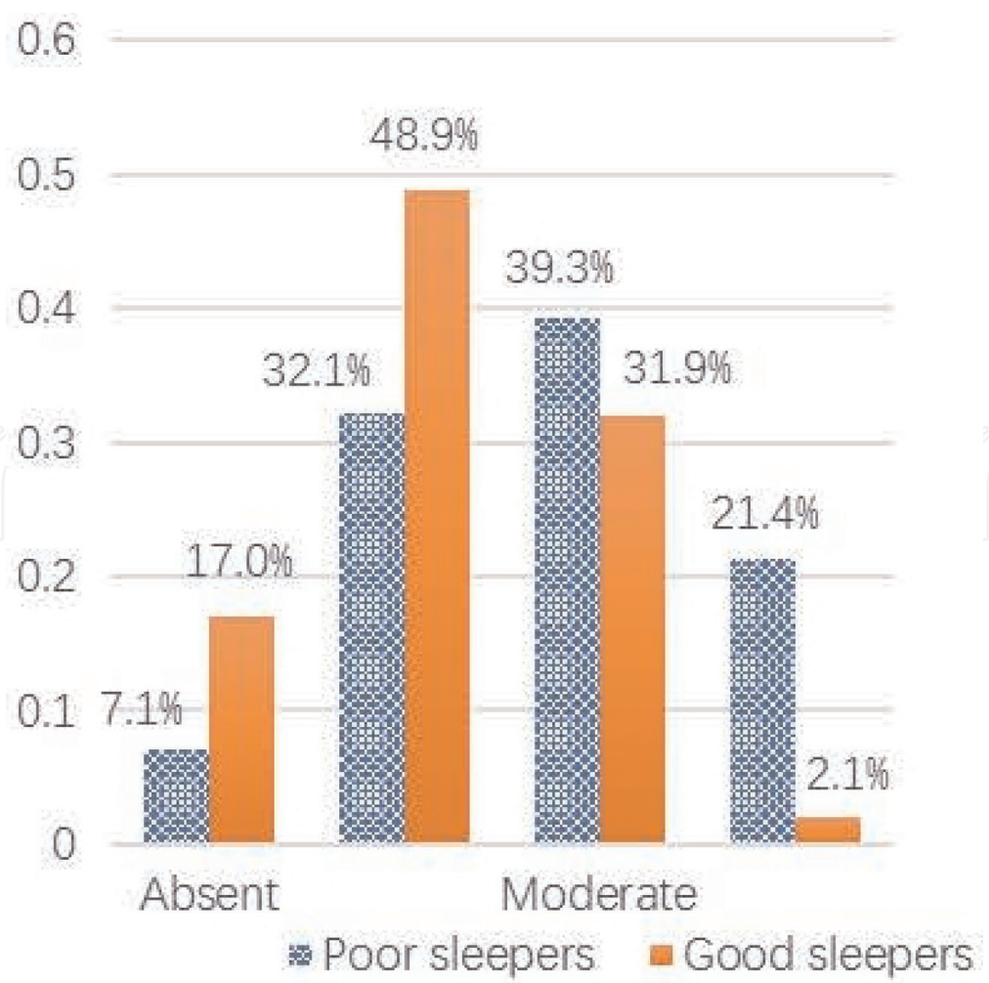


Figure 2.
Sleep quality comparison among different CMS severity at 3996 altitude. Modified from Kong et al. [4].

For people with CMS stationed at Tibet, the proportion of poor sleepers (defined as PSQI > 5) with severe CMS was 12.54-fold higher than that of good sleepers. See **Figure 2**, CMS severity comparison between "good" and "poor" sleepers at 3996 m altitude. Subjects with CMS had higher scores in each sleep component of the PSQI score, except the use of sleep medication. After adjusted for CMS score, age, and education, poor sleep quality was determined to be an independent predictor of impaired intelligence quotient [odds ratio (OR) 1.59, 95% CI 1.30–1.95] and short-term memory (OR 1.18, 95% CI 1.07–1.31). Therefore, for people with CMS, the poorer the sleep quality, the worse was the cognitive function [4].

4. Variation of sleep architecture at high altitude

Polysomnography (PSG) is the gold standard for investigating sleep architecture. However, the technical complexity and logistic demands had brought restriction on its utilization during altitude studies. Although there are several studies that suggest wrist actigraphy-derived data on total sleep time, sleep efficiency and sleep onset latency were similar to those of PSG [24]; actigraphy is insufficient in detecting sleep stage and breathing events.

Objective assessment of sleep architecture at altitude by electroencephalogram was first reported by Joern et al. in 1970 [25]. They found a near absence of stages 3 and 4 and a 50% reduction in rapid eye movement (REM) sleep and reported PB and arousals in one subject. A later study in 1975 confirmed a decrease in deeper sleep and increase in lighter sleep stages and brief arousals after ascending to an altitude of 4300 m at the Pikes Peak when compared to subjects at low altitude [26]. Subsequent studies have generally confirmed the shift at altitude toward lighter sleep stages, with a variable change in duration of REM sleep and increased awakenings associated with PB [27–30].

Alterations in objective sleep parameters have also been observed during acclimatization. A recent literature review on high-altitude sleep concludes that during rapid ascent to high altitude, there is a reduction in total sleep time, sleep efficiency, and deep sleep (stages 3 and 4) (in new nomenclature N3) and a significant increase in arousals and PB [31]. These variations are possibly high altitude dependent, and the effects tend to moderate with acclimatization [6]. Hypnograms of a partially acclimatized lowlander sleeping and a native Tibetan sleeping at high altitude are shown in **Figures 3** and **4**.

Although subjective sleep quality is impaired at high altitude, attempts to find a correlation between objective and subjective measures have failed to find a connection [24]. One study investigated 63 participants who completed a 3-hour flight from sea level to the South Pole (3200 m) and discovered no association between self-reported sleep quality and sleep efficiency, nocturnal oxygen saturation, and apnea/hypopnea index (AHI) obtained from PSG [32]. When assessed by LL score, there was no significant correlation of the subjective sleep measurement compared to sleep efficiency derived from PSG and actigraphy [24]. Another study investigated 165 young male soldiers stationed in Tibet Plateau (3800 m) for at least 3 months. In a multiple regression model adjusted for age, service time, body mass index, Epworth Sleepiness Scale, anxiety, and depression, sleep onset latency (b = 0.08, 95% CI: 0.01–0.15) and NREM latency (b = 0.011, 95% CI: 0.001–0.02) obtained from PSG were slightly positively correlated with global PSQI, while mean nocturnal SpO_2 (b = −0.79, 95% CI: −1.35 to −0.23) and time in stage 3 + 4 sleep (b = −0.014, 95% CI: −0.001 to −0.028) was slightly negatively associated with global PSQI [12].

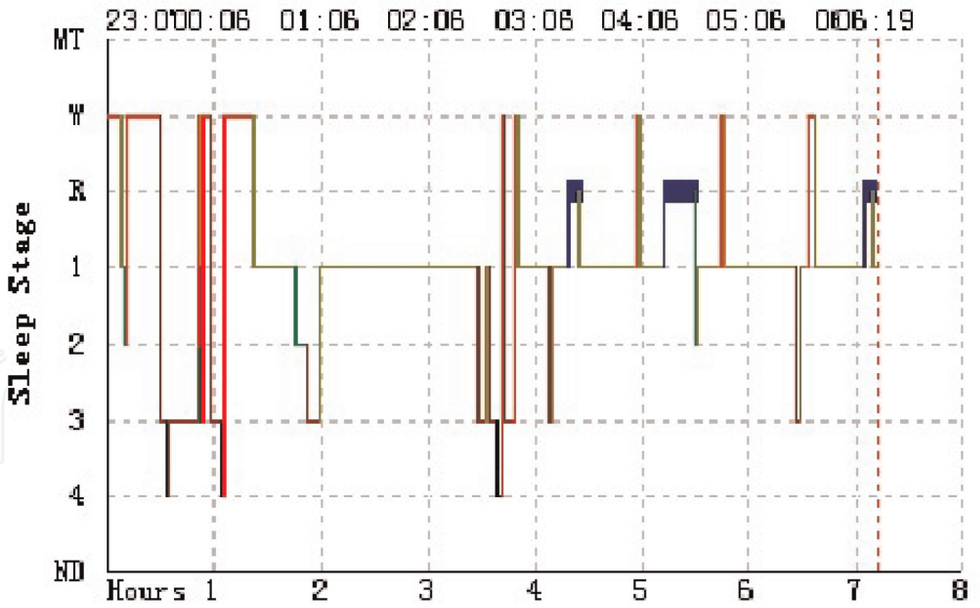


Figure 3.
Hypnogram of a 27-year-old young man sleeping acclimatized for 11 months at altitude of 3800 m. Frequent awake, less proportion of stage 4 and REM sleep might be observed.

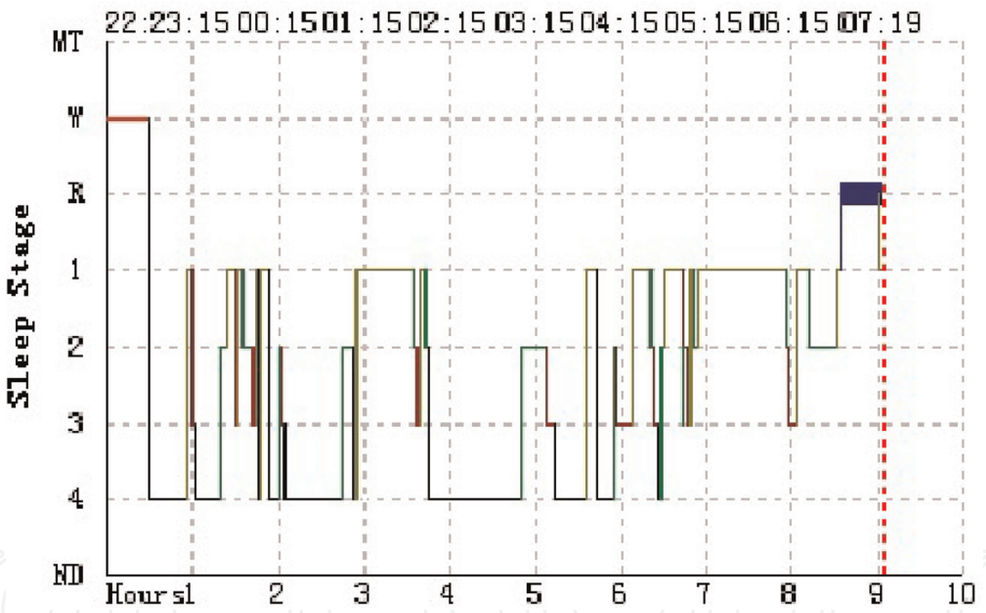


Figure 4.
Hypnogram of a 25-year-old native Tibetan sleeping at altitude of 3800 m. There is sufficient time in stage 4 sleep and scarce REM sleep.

5. Differences in sleep architecture between lowlanders and native highlanders at high altitude

5.1 Sleep patterns of high-altitude natives

Tibetans and Andeans are the native populations to the Tibetan and Andean Plateaus descending from colonizers. Both populations have been exposed to the hypoxic environmental stress of lifelong exposure to high altitude. But native Tibetans and Andean highlanders exhibit different ways of adaptation to chronic hypoxia [33]. Andean highlanders have blunted hypoxia ventilatory response

compared to Tibetans which is thought to be acquired and developed in adolescence [34]. Native Tibetans were reported to have higher maximal oxygen uptake, greater ventilation, and brisker hypoxic ventilatory responses to adapt to the hypoxic environment at high altitude and, therefore, to have a better-quality sleep than Han lowlanders [35] which may largely be attributed to genetic adaptations [36].

Few studies had compared sleep architecture between high-altitude dwellers and non-native highlanders. An elder study investigated the Sherpa highlanders dwelling above 3500 m. The Sherpas exhibited few PB with apnea due to low ventilatory sensitivity to hypoxia at 5300 m altitude [37]. A later study reported the sleep pattern of Peruvian Andeans situated at 4330 m altitude. Sleep architecture is closely resembling to normal of people at sea level with significant amount of NREM sleep and unimpaired REM sleep [38]. Contrary to the previous reports, a recent study surveyed sleep architecture of Peruvian highlanders living in Puno at 3825 m. The highlanders had a longer time in total sleep time and increased wake-after-sleep onset and arousal index but decreased sleep efficiency, which suggest greater disturbances in sleep in highlanders compared with lowlanders [39].

5.2 Sleep architecture in partially acclimatized lowlanders

As we mentioned above, acclimatization would help lowlanders to relieve sleep disturbance after ascending to high altitude. This could be supported by an earlier study which claimed over 3 days of acclimatization over 4559 m resulted in a partial recovery of sleep structure with increases in slow wave sleep and REM sleep and a reduction in the arousal index [40].

But little is known whether prolonged hypoxia may help to improve sleep architecture at high altitude. Animal studies showed that there was a 50% reduction in the proportion of slow wave sleep and loss of REM sleep when rats were chronically exposed to hypoxia environment simulating an altitude of 5000 m [41, 42]. A clinical study conducted in Shangri-La, which has an altitude of 3800 m, surveyed the differences in sleep architecture between native Tibetans' and Han lowlanders' stations for at least 3 months. After adjusted for the length of stay at altitude, significant differences in lower mean nocturnal SpO_2 and shorter time in NREM sleep were determined in acclimatized lowlanders than the native Tibetans [12]. **Figure 5** indicates a decreased nocturnal artery oxygen of a 3-month acclimatized lowlander. So, it is reasonable to conclude that the effect of prolonged acclimatization to hypoxia is limited in relieving hypoxemia and improving deep sleep which might be an explanation for the impaired cognition brought about by poor sleep.

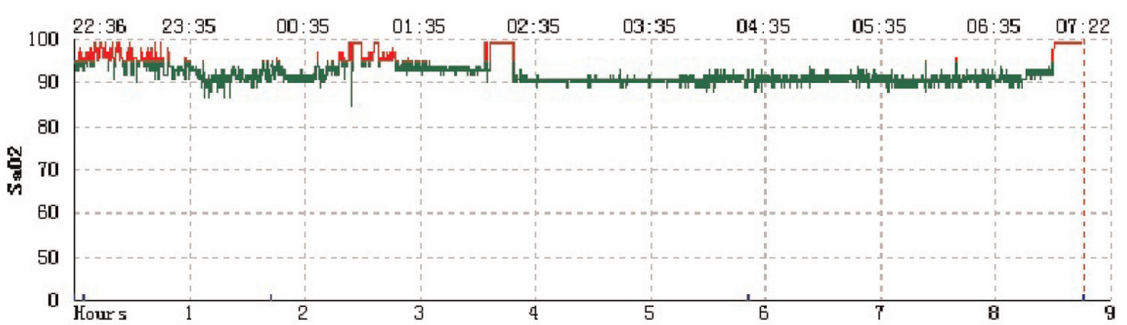


Figure 5.
Decreasing in artery oxygen during sleep of a 24-year lowlander acclimatized for 3 months at 3800 altitude. The lowest SaO_2 is 83% and the mean SaO_2 is 92%.

6. Is sleep disorder an altitude-related illness?

Studies on sleep disorder at high altitude from the above reviewed scientific literature confirm the assumption that altitude-related illness including AMS and HAPE may deteriorate sleep quality either directly or indirectly through complaints of headache, hard breathing, cough, etc. It is widely accepted that HAPE usually develops within 2–4 days after quickly ascending to high altitude, but sleep in the first night at altitude may have been affected. Both susceptible HAPE subjects and healthy mountaineers without HAPE revealed a major reduction in sleep efficiency and in NREM stage 3 and 4 sleep (in new nomenclature N3) in the first night after the ascent to 4559 m within 1 day [43]. The deteriorated ventilation and intermittent hypoxia associated with PB in the first 1–2 nights at high altitude with the associated elevation of pulmonary artery pressure may promote the subsequent development of HAPE in susceptible subjects. Thus, the occurrence of sleep disorder is prior to and/or independent of HAPE but may worsen due to HAPE.

Literature reports also provide empirical evidence that sleep disturbance was discordant from other AMS symptoms and absent in 40% of cases with severe headache, long considered a symptom of AMS. Since sleep disorder correlated poorly with other symptoms of AMS, the sleep component had been removed from the 2018 Lake Louise Acute Mountain Sickness Score [44].

Therefore, it is conceivable that sleep disorder should be viewed as an independent altitude-related illness rather than a symptom of AMS despite the fact that it may overlap other mountain sicknesses. In accordance with the nomenclature of other high-altitude diseases [e.g., high altitude cerebral edema (HACE), high altitude pulmonary edema (HAPE), etc.], high-altitude sleep disorder (HASD) might be an appropriate name.

7. Treatment of HASD

Hypoxemia is the main reason and one of the primary independent contributors to poor sleep quality at high altitudes [12]. In theory, correction of hypoxemia by supplemental oxygen or pharmacological suppression of ventilation may have the potential in treating sleep disorder at high altitude.

7.1 Supplemental oxygen

A case report tested the treatment effect of a nasal demand oxygen delivery device on hypoxemia during sleep at high altitude in a 46-year-old male healthy participant at an altitude of 4600 and 5700 m [45]. The participant received a volume of oxygen delivery dose for 0, 16.7, 33.3, and 50 ml/s at random per pulse for every 2 h during sleep period. Results of the study indicated an increase in arterial blood oxygen saturation and decreases in tidal volume and AHI.

Another controlled trial employed a noninvasive ventilation mode named adaptive servo ventilation (ASV) to stabilize periodic breathing due to hypobaric hypoxemia at an altitude of 3800 m, but it failed to affirm its efficacy in controlling central sleep apnea during sleep. However, in their controlled group, supplemental oxygen improved oxygen desaturation index and oxygen saturation, whereas it reduced the arousal index and NREM stage 1 sleep. But neither ASV nor supplemental oxygen could improve subjective quality as measured by the Stanford Sleep Questionnaire and LL score [46].

In summary, based on current limited studies, supplemental oxygen does improve arterial blood oxygen saturation but could not result to a better sleep quality.

7.2 Diet therapy

Dietary nitrate (NO^{3-}), which is found in beetroot and other vegetables, and inorganic NO^{3-} salts have been shown to have vasodilatory properties [47] and also to reduce oxygen uptake during exercise [48], suggesting NO^{3-} supplementation might play a physiological role during sleep at high altitude. A single-blind placebo-controlled trial examined the effects of dietary NO^{3-} supplementation on the degree of sleep-related hypoxemia in healthy subjects at an altitude from 3700 to 4900 m. Each subject received two 70 ml shots of either beetroot juice (~5.0 mmol NO^{3-} per shot) or placebo (~0.003 mmol NO^{3-} per shot) over two consecutive nights at altitude. Results of the study favored dietary nitrate in increasing fluctuations in arterial O_2 saturation during sleep at altitude in native lowlanders, but it does not improve AHI or oxygenation [49].

7.3 Pharmacological agents

Previous reports suggested that only a few medications may be helpful at high altitudes [50, 51], including theophylline, acetazolamide, zolpidem, zaleplon, temazepam, and integripetal rhodiola herb, a traditional Chinese herb. However, there are often several limitations on pharmacological selection at high altitudes in clinical practice, as current sleeping medications prescribed for sleep disturbances at sea level are not suggested to be used at altitude. For example, it is widely accepted that benzodiazepines (BZDs) may cause hypoventilation, triggering respiratory abnormalities during sleep [52–54]. Therefore, an ideal choice for medication use at high altitude should neither deteriorate ventilation and oxygen saturation nor affect sleep architecture.

7.3.1 Acetazolamide

Acetazolamide is considered to increase ventilation and oxygenation, effectively reducing PB by approximately 50% [55]. A meta-analysis of randomized controlled trials determined that acetazolamide improves sleep apnea at high altitude by decreasing AHI and percentage of PB time and increasing nocturnal oxygenation. Results from clinic trials also suggested that a 250 mg daily dose may be as effective as higher daily doses for healthy trekkers [56].

7.3.2 Non-benzodiazepines

The efficacy and safety of zolpidem and zaleplon in treating sleep disturbances at high altitude had been confirmed by several well-designed clinic trials [57–60]. A recent meta-analysis of randomized placebo-controlled trials revealed that zaleplon and zolpidem improved the total sleep time, sleep efficiency, and stage 4 sleep duration, whereas they decreased the wake-after-sleep onset without impairing ventilation [61] (data are shown in **Figure 6**).

There was no significant difference in ventilation as measured by SpO_2 and PB between participants administered with zaleplon or zolpidem and placebo [58–60]. Furthermore, participants who were administered with zaleplon or zolpidem expressed a significant improvement in the subjective sleep quality, which was

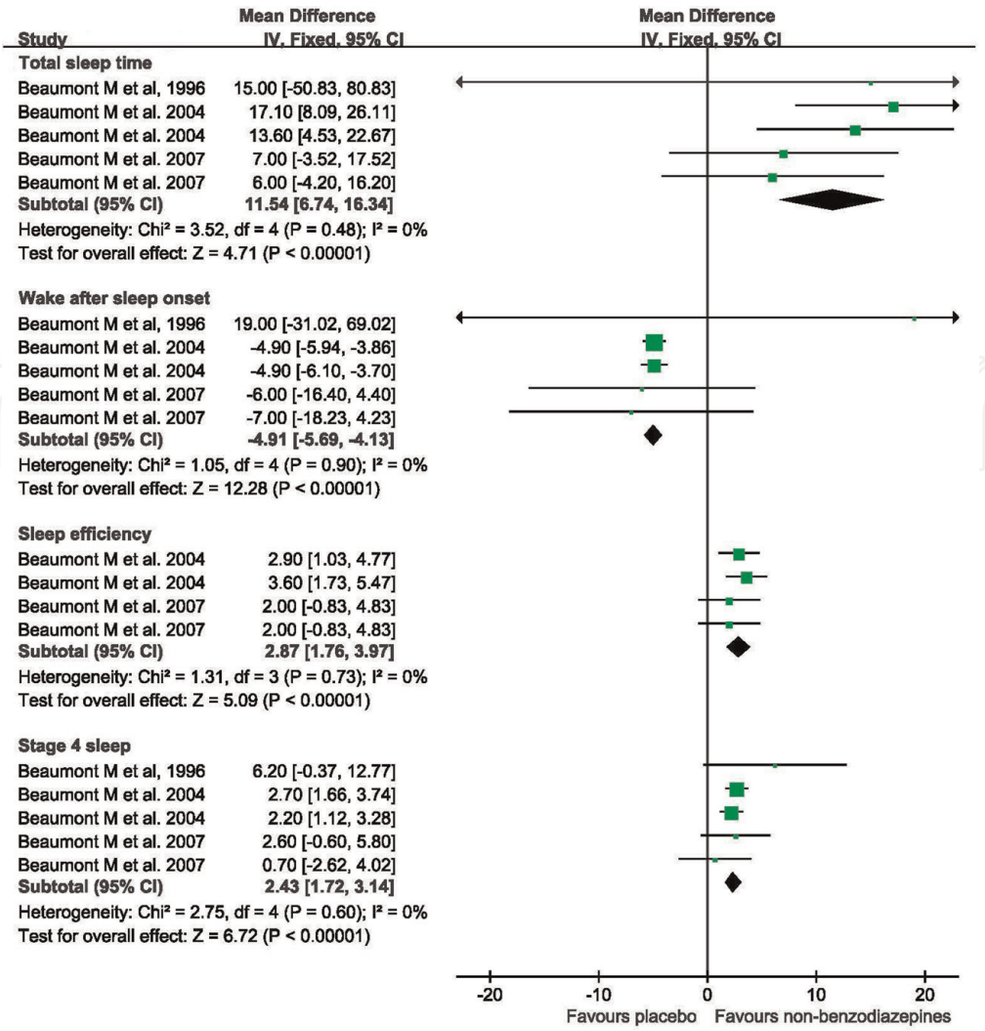


Figure 6.
Summary of non-benzodiazepines in improving sleep architecture at high altitude. Modified from Kong et al. [61].

measured by sleep log question [59, 60] and PSQI (4.15 ± 2.76 in zolpidem group vs. 6.58 ± 3.98 in placebo group, P = 0.047) [60].

7.3.3 Benzodiazepines

Benzodiazepine use in this environment is controversial. Early studies showed that 1 mg of oral loprazolam did not worsen either slow wave sleep depression or apnea and allowed normal sleep reappearance after acclimatization [28, 62]. Later, a randomized, double-blind, placebo-controlled trial conducted at 3000 m altitude validated PaO_2 decreasing and $PaCO_2$ increasing significantly 1 hour after 5 mg of oral diazepam [63], which suggests that it may cause hypoventilation.

On the contrary, temazepam, a short-acting benzodiazepine, was recommended to be safely used by the International Climbing and Mountaineering Federation MedCom Consensus Guide [51]. However, the effect of temazepam on the objective sleep parameters was inconsistent. Nicholson et al. [64] reported that temazepam significantly shortened the mean sleep onset latency and increased the amount of the REM sleep, whereas Nickol et al. [65] reported no differences in the actigraphy-derived sleep parameters. Results on oxygen saturation and PB from the aforementioned studies were also inconsistent. When compared to the placebo, temazepam showed no significant effect on mean oxygen saturation, yet PB significantly decreased [66]. Although Nickol et al. [65] reported that temazepam could decrease

median oxygen saturation, it did not significantly reduce PB during sleep. Because of the inconsistencies in the reported variables, no confirming conclusions can be drawn from available evidence.

To sum up, the use of benzodiazepines should be discouraged at high altitude due to the nocturnal hypoventilation nature of these agents. The efficacy and safety of temazepam need further confirmation by well-designed placebo-controlled trials.

7.3.4 Others

Additional drugs that may be helpful reported by case series include theophylline and the integripetal rhodiola herb, which is a widely used traditional Chinese herb in Tibetan areas. However, strong clinical evidence from randomized controlled trials supporting the effectiveness and safety of these agents has not been demonstrated.

7.4 Recommendations

Evidence from current available studies support the routing use of supplemental oxygen during sleep to increase arterial blood oxygen saturation. Acute dietary NO^{3-} supplementation reduces flow limitation and induces more pronounced SaO_2 desaturations during sleep at high altitude. Acetazolamide at 250 mg daily dose is effective in reducing sleep apnea, decreasing AHI and PB, and increasing nocturnal oxygenation. Both zaleplon and zolpidem improved the objective sleep architecture without impairing ventilation.

8. Conclusions

Our understanding on sleep disorder at high altitude is still limited. Mountain tourists commonly complain about subjective sleep disturbances with difficulty in onset of sleep and frequent awakenings in the first few nights at altitude. But those subjective sensations of poor sleep neither are associated with severity of mountain sickness nor tend to disappear after long exposure to high altitude. And consequently, cognitive function was impaired.

There is no reliable evidence that support the consistency between self-report sleep quality and sleep parameters obtained from PSG. The most frequently reported changes in sleep architecture at high altitude are detected by PSG including a decrease in NREM sleep and occurrence of PB. Different patterns of adoption to hypoxic environment exist among native highlanders. For lowlanders ascending to high altitude, acclimatization would be beneficial in relieving hypoxemia and improving deep sleep; however, PB would not be largely relieved after acclimatization.

The occurrence of HASD is prior to most altitude-related diseases and would last for a longer time. We strongly suggest future study to consider it as an independent high-altitude illness as it had been removed from the diagnosing and managing of AMS by the International Society of Mountain Medicine World Congress Committee.

The treatment principle of HASD should not deteriorate nocturnal ventilation and SaO_2 or affect sleep architecture. The following evidence-based choices are recommended. Effective treatments for altitude-related nocturnal hypoxemia include dietary NO^{3-} supplementation before sleep and supplemental oxygen during sleep. Medication for respiratory disturbance is 250 mg daily dose of oral acetazolamide, which is beneficial in relieving sleep apnea, decreasing AHI and PB, and promoting nocturnal oxygenation. Both zaleplon and zolpidem are optional agents in improving the objective sleep architecture and subjective sleep quality without impairing ventilation.

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