Mini review

Sleep at high altitude: guesses and facts

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Abstract

Lowlanders commonly report a poor sleep quality during the first few nights after arriving at high altitude. Polysomnographic studies reveal that reductions in slow wave sleep are the most consistent altitude induced changes in sleep structure identified by visual scoring. Quantitative spectral analyses of the sleep electroencephalogram have confirmed an altitude related reduction in the low frequency power (0.8-4.6 Hz). Although some studies suggest an increase in arousals from sleep at high altitude this is not a consistent finding. Whether sleep instability at high altitude is triggered by periodic breathing or vice-versa is still uncertain.

Overnight changes in slow wave derived encephalographic measures of neuronal synchronization in healthy subjects were less pronounced at moderately high (2590 m) compared to low altitude (490 m) and this was associated with a decline in sleep related memory consolidation. Correspondingly, exacerbation of breathing and sleep disturbances experienced by lowlanders with obstructive sleep apnea during a stay at 2590 m was associated with poor performance in driving simulator tests. These findings suggest that altitude related alterations in sleep may adversely affect daytime performance. Despite recent advances in our understanding of sleep at altitude further research is required to better establish the role of gender and age in alterations of sleep at different altitudes, to determine the influence of acclimatization and of altitude related illness, and to uncover the characteristics of sleep in highlanders that may serve as a study paradigm of sleep in patients exposed to chronic hypoxia due to cardiorespiratory disease.

Keywords: altitude, hypoxia, sleep, insomnia
**Introduction**

Worldwide an increasing number of persons is travelling to altitude for professional and leisure activities, and several millions of people permanently reside in mountain areas at high altitude (8; 16). Whether and to which extent acute or chronic exposure to hypobaric hypoxia at altitude affects sleep, an essential element of human well-being, is still uncertain. Relatively few scientific studies have investigated the impact of altitude exposure on subjective sleep quality and on characteristics of sleep measured by objective means. Presumably, the sleep of travelers arriving from lowlands at high altitude is poor in the first few nights but improves with acclimatization (33). Whether sleep is disturbed by a direct effect of the reduced barometric pressure and the consecutive hypoxia, or whether other factors play an important role including the excitement or stress of being in an unusual environment, physical stimuli such as noise, uncomfortable temperature and sleeping conditions, is uncertain (34). Moreover, high altitude periodic breathing, a pattern of breathing with waxing and waning of ventilation that commonly occurs even in healthy persons at elevations above 1500 m, and acute altitude related illness may also affect sleep (14). Insomnia has been considered a manifestation of acute mountain sickness (43) although this has been challenged recently (15; 28).

Despite the common belief that sleep quality at altitude is poor, the scientific evidence to support this notion is still modest. Based on observational studies, many of them performed in only a few healthy young men, it has been assumed that the main changes in sleep structure at altitude consisted in a reduction of deep sleep and an impairment of sleep continuity (figure 1). These concepts have been endorsed by several narrative reviews (42; 54; 55). Recent investigations including a few randomized trials have provided more robust and quantitative data on the changes of sleep at high altitude. The purpose of the current work was therefore to perform a systematic analysis of the scientific literature on sleep at altitude in...
order to summarize the established facts and to identify areas that might benefit from a corroboration of current assumptions by further research.

The topics that we address specifically include characteristics of sleep in newcomers at high altitude, changes in sleep during altitude acclimatization, treatments of altitude induced sleep disturbances, sleep in patients with respiratory disease travelling to altitude, and sleep in highlanders.

Systematic search of the literature

A systematic search of the literature was performed (last retrieval on May 30, 2015) using the PubMed and the MEDLINE database (http://www.ncbi.nlm.nih.gov/pubmed/). The search terms and the number of returned articles are listed in table 1. Titles and abstracts of the retrieved publications were studied. Articles were further analyzed if the following criteria were met: original investigations in adult humans; sleep assessment by either polysomnography, actigraphy or standardized questionnaires; the study design, altitude and setting were reported; the results with appropriate statistics were reported. Data from these studies are described in this minireview.

A further, detailed analysis of all studies using polysomnography in at least 10 participants in addition to fulfilling the criteria mentioned above was performed. The results of this analysis are presented in the tables 2-4. The minimally required number of 10 participants was derived by a power calculation assuming a minimal important difference of 5% in slow wave sleep, a SD of 7%, a power of 0.8 and an alpha level of 0.05 based on data from a previous study (24).

The literature research provided 14 original publications with data from nocturnal polysomnography at altitude. Two of these (5; 30) used a hypobaric chamber to simulate altitude exposure, the other 12 studies were field studies (11 performed in the Alps and 1 in
Taiwan (52)). Ten of the 14 papers reported data on healthy subjects and 4 on patients with obstructive sleep apnea. Due to the inhomogeneity of the studies a pooled analysis was not feasible. The study design and setting, the Oxford Center of Evidence-Based Medicine evidence level (40), the number of participants, and the main outcomes were extracted and tabulated for these polysomnographic studies.

**Sleep in newcomers at altitude**

Questionnaire evaluations suggest that sleep disturbances at high altitude are common. For example, 46% of 100 Iranian ski tourists reported frequent awakenings and other subjective sleep disturbances (Groningen insomnia score >6) they perceived in the first night after arriving at a hotel at 3500 m (17). Similarly, among 305 Chinese soldiers transported from 500 m to 3700 m in Lhasa, 32% suffered from insomnia in the first night at altitude (Athens insomnia scale score ≥6), and 74% of 246 workers air lifted to the South Pole at 2835 m reported difficulty sleeping in the first week (1). As subjective perception and neurophysiologic correlates of sleep may differ considerably at altitude (36) it is important to consider both subjective reports and objective assessments when evaluating altitude effects on sleep.

The results of our systematic analysis of the literature on polysomnographic sleep studies in newcomers at altitude is provided in Tables 1-4. In the largest study evaluating alterations in sleep structure induced by travelling to altitude (i.e., ascent from 490 m, to 1630 m, and 2590 m) the main changes observed in 51 healthy young men (median age 24 y) included a slight reduction in deep sleep (figure 2, panel A), i.e., a reduction of 3% in non-rapid eye movement (NREM) sleep stages 3 and 4 at 2590 m, but no significant changes in sleep efficiency and arousals (24). In the same study, power density spectra of frontal and central electroencephalogram derivations revealed a reduction in slow wave activity (0.8-4.6
Hz) during NREM sleep by ~4% in the first night at 1630 m and by ~15% at 2590 m (figure 2, panel B) (48); additional altitude related changes that have not been described previously, included a decrease in theta (4.6 to 8.0 Hz) activity and an increase in spindle peak height and frequency at 2590 m. Reductions in slow wave and theta activity were also noticed during rapid eye movement (REM) sleep (48). Nevertheless, subjective sleep quality was not significantly impaired, and daytime tests of vigilance and cognitive performance did not reveal any altitude related decrements at 1630 m and 2590 m (24). A more pronounced reduction in deep sleep was observed in other studies performed at higher altitude, i.e., a 12% reduction in NREM stages 3 and 4 at 4559 m along with a 5% reduction in REM sleep associated with subjective insomnia and symptoms of acute mountain sickness reported by the mountaineers (39).

Early studies have suggested that a pronounced sleep fragmentation was a characteristic change occurring with exposure to hypobaric hypoxia (2). However, these observations obtained in only 5 subjects confined to a hypobaric chamber for several weeks while being exposed to extremely low barometric pressure are not likely to reflect the conditions of the majority of mountain tourists. Recent field studies revealed an only modest increase in the number of arousals at high altitude, i.e., 17.9 arousals/h in the first night at 4559 m compared to 5.4/h at 490 m (39); and 24.2 arousals/h at 3150 m compared to 20.7/h at 9 m (52). At moderate altitude, no increase in the number of nocturnal arousals was observed (7.7 arousals/h at 2590 m vs. 8.3/h at 490 m)(24). Whether high altitude periodic breathing triggers arousals from sleep or, vice versa, sleep fragmentation promotes instability of ventilatory control remains controversial. Both spontaneous arousals not associated with central apnea and arousals following apneas of periodic breathing have been described (19). However, the observation that the amount of high altitude periodic breathing in mountaineers arriving at 4559 m increased with acclimatization over the course of 3 nights (i.e., the apnea/hypopnea index increased from 60.9/h in the 1st to 86.5/h in the 3rd night at 4559 m)
while the arousal index decreased over the same period (from 17.9/h to 5.7/h) suggests independent physiologic mechanisms (39). Correspondingly, in healthy newcomers at 2590 m, the arousal index determined by visual EEG analysis was not different from that at 490 m (i.e., 7.7/h at 2590 m vs. 8.3/h at 490 m) although the apnea/hypopnea index had increased significantly (13.1/h at 2590 m vs. 4.6/h at 490 m) (24). Quantitative electroencephalogram analysis in the same study revealed that spectral EEG signatures during periodic breathing without visually scored arousals were similar to those of sleep periods without periodic breathing but with visually scored arousals (46; 49). Therefore, high altitude periodic breathing seems to be associated with EEG alterations not apparent during visual inspection using standard criteria (46). Subtle changes in electrical brain activity induced by exposure to even mild hypobaric hypoxia may thus reflect cortical dysfunction at altitude. Sophisticated, quantitative measurement techniques are required to detect these effects.

Consistent with an unfavorable effect of altitude on sleep, overnight changes in slow wave derived measures of neuronal synchronization (i.e., overnight decrements in the slope of slow waves) were less pronounced at 2590 m than corresponding baseline measures at 490 m and this was associated with a decline in the sleep related memory consolidation assessed by a visual-motor learning task (figure 2, panel C) (51). Impairment in postural control observed at 2590 m during the same study further supports a role of even mild hypoxia and possibly sleep disturbances in causing central nervous performance decrements (47) even though vigilance and cognitive function were not noticeably affected in certain tests (24). In turn, studies performed at higher altitude (3800 m and 3900 m) have revealed cognitive impairment and improvement of sleep and periodic breathing by nocturnal oxygen enrichment that were followed by subsequent improvements in day-time performance in neuropsychological tests (26; 27).
Changes in sleep during altitude acclimatization

Data on the effects of altitude acclimatization on sleep structure are very scant (Table 3). In healthy mountaineers ascending rapidly from 490 m to 4559 m a reduction of total sleep time, sleep efficiency, deep sleep (NREM stages 3 and 4) and a significant increase in arousals and pronounced periodic breathing were noted in the first night at high altitude (39). The changes in sleep structure were partially normalized in the third night at 4559 m in association with an improvement in nocturnal arterial oxygen saturation while periodic breathing increased even further (39). At an altitude of 3150 m (52) and at 2590 m (24), no significant changes in sleep structure between the first and second nights were noted. Based on the cited studies (24; 39; 52) one might hypothesize that the effects of acclimatization on sleep are altitude dependent. In this context it is interesting to note that the progression or regression of high altitude periodic breathing during acclimatization seems also to depend on the altitude: Thus, at 4559 m (39) and at altitudes from 4497 m to 6825 m (6), the amount of high altitude periodic breathing (expressed as apnea/hypopnea index or percent of the nighttime with periodic breathing) increased with the time spent at altitude (6). Conversely, in studies at 1650 m and 2590 m (24) and at 3450 m (20) high altitude periodic breathing decreased from the first to the second night. Assuming a sleep disruptive effect of high altitude periodic breathing (as discussed above), these observations offer a possible explanation of the altitude dependent differential effect of acclimatization on sleep structure. The varying tendency to breathing instability (periodic breathing) during the initial and prolonged exposure to moderate or high altitude may be related to changes in the balance between the ventilatory sensitivity to hypoxia and hypocapnia (12). In other studies that reported repeated sleep studies in lowlanders during more prolonged sojourns at higher altitudes the independent effect of acclimatization was difficult to assess because of
progressive increases in altitude over the course of a trek in the Himalayas (18) or because of inadequate sample size and non-standardized sleep scoring (44).

Sleep disturbances in altitude related illness

It is conceivable that altitude related illness including acute mountain sickness and high altitude pulmonary edema may interfere with refreshing sleep either directly or through symptoms such as headache, cough and shortness of breath although there is little robust evidence to corroborate this (Table 2-4). Mountain travelers with acute mountain sickness at 3250 m had a minor reduction in REM sleep but an otherwise similar sleep structure compared to controls without acute mountain sickness (52). High altitude pulmonary edema susceptible subjects revealed a major reduction in sleep efficiency and in deep sleep (NREM 3 and 4) in the first night after ascent to 4559 m within less than 24 h (Table 4) (38). These changes were similar to those in mountaineers without known susceptibility to high altitude pulmonary edema in the same setting (Table 2) (39). Since high altitude pulmonary edema usually develops within 2-4 days after rapid ascent, sleep in the first night at altitude may not have been affected in the participants of the cited study although subtle changes in the nocturnal breathing pattern, i.e., an increase in the breath rate and periodic breathing, were noted (9). The combination of sustained and intermittent hypoxia associated with periodic breathing in the first 1-2 nights at high altitude with the associated surges of pulmonary artery pressure may promote the subsequent development of high altitude pulmonary edema in susceptible subjects.

Treatment of altitude induced sleep disturbances

Several studies have evaluated the effect of hypnotic drugs on altitude induced sleep disturbances but only few used polysomnography (Table 4). In a randomized, placebo-
controlled hypobaric chamber study simulating an altitude of 4000 m (3), and a field study in the French Alps at 3610 m (4), the GABA\textsubscript{A} agonists zaleplon (10 mg) and zolpidem (10 mg) were evaluated. Zolpidem provided minor although statistically significant improvements in deep NREM sleep (i.e., a 2.6% increase in stage 4 vs. placebo). No impairment of nocturnal oxygen saturation, breathing pattern or daytime performance in cognitive test batteries were noted with either zaleplon or zolpidem compared to placebo (3; 4). In a study performed in Nepal at 3540 m, 34 trekkers received either temazepam (7.5 mg) or acetazolamide (125 mg) in the first night at that altitude according to a randomized, double-blind design (50). Participants receiving temazepam reported a better subjective sleep quality and less frequent awakenings to urinate than those receiving acetazolamide. No polysomnographic data were available in that study (50). In climbers staying at Everest base camp at 5300 m, temazepam (10 mg) improved subjective sleep quality and reduced the cyclic oxygen desaturations due to periodic breathing compared to values during a placebo night without affecting mean nocturnal oxygen saturation (13). But temazepam (10 mg) did not improve subjectively perceived insomnia nor actigraphic indices of sleep continuity in 19 trekkers sleeping at 5000 m in Nepal compared to a control group of 14 trekkers receiving placebo (31). Interpretation of these results is hampered by incomplete data sets, and the small number of participants, some of them also taking acetazolamide.

In high altitude pulmonary edema susceptible mountaineers, dexamethasone (2x8 mg/d) taken before a rapid ascent to 4559 m resulted in a better subjective sleep quality and a greater total sleep time and sleep efficiency recorded by polysomnography in the first night at altitude compared to participants not receiving the drug (Table 4) (38). Taking dexamethasone before ascent increased the mean nocturnal oxygen saturation and reduced the heart rate at 4559 m which is consistent with the beneficial effects of dexamethasone on reducing pulmonary artery pressure and preventing overt high altitude pulmonary edema (29).
Sleep in patients with respiratory disease travelling to altitude

Although patients with disturbances of control of breathing or gas exchange impairment due to respiratory disease may be particularly susceptible to adverse effects of hypobaric hypoxia at altitude there has been little scientific evidence to counsel these patients regarding the risks of altitude travel and effective measures to prevent them. To address this point, we have performed several randomized, controlled trials in lowlanders with obstructive sleep apnea syndrome (OSA) (Tables 2-4) (25; 35; 37; 53). These studies revealed that OSA patients who discontinued their continuous positive airway pressure therapy when staying in Alpine resorts at an elevation of 1860 m and 2590 m had pronounced nocturnal hypoxemia and an exacerbation of sleep apnea due to frequent central events (37). This was associated with a reduced cerebral tissue oxygenation (53), decreased sleep efficiency and deep sleep, and more frequent arousals compared to nights at 490 m (37; 53). Moreover, driving simulator performance during daytime was impaired at altitude (37). Continuous positive airway pressure treatment with computer controlled mask pressure (AutoCPAP) combined with acetazolamide improved arterial oxygen saturation and prevented the altitude induced increase in sleep apnea (25). Another trial suggested that acetazolamide alone may be beneficial for patients with obstructive sleep apnea travelling to remote mountain areas where CPAP therapy is not feasible as it improved arterial and cerebral oxygenation, central sleep apnea, and prevented excessive blood pressure rises. These studies in obstructive sleep apnea patients have been reviewed recently (7; 21).

Preliminary studies revealed that lowlanders with chronic obstructive pulmonary disease (COPD, GOLD grade 2-3) who were normoxemic and did not have sleep apnea at 490 m were significantly more hypoxemic and developed moderate to very severe, predominantly
central sleep apnea with reduced sleep efficiency and deep sleep when staying at 1650 m and 2590 m compared to 490 m (23).

Thus, current evidence suggests that patients with obstructive sleep apnea or COPD at lowlands are particularly susceptible to periodic breathing and sleep disturbances when staying at altitude. No other robust data on sleep in altitude travellers with preexisting respiratory or cardiac conditions are available.

Sleep in highlanders

Virtually no conclusive data on sleep characteristics in highland residents are available. Normand et al. (32) reported that sleep organization assessed in Bolivian highlanders in La Paz at 3850 m was “roughly” similar in 14 highlanders with polycythemia compared to 6 without polycythemia but no comparison to measurements in lowlanders was provided. Cote et al. (11) performed polysomnographic studies in 8 Peruvian highlanders (mean hematocrit 58%) at Cerro de Pasco (4330 m). Sleep efficiency was 91%, the relative duration of deep sleep (NREM stages 3 and 4) was 26%. Again, no comparison to data from lowlanders was performed in the cited and in a similar additional study performed by the same group (10). In Indian soldiers, 6 of them Ladakhis born and brought up at 3300-3800 m, sleep studies were obtained at an altitude of 3500 m but the data are inconclusive because of the small sample size (45). Our own preliminary data from a study in Kyrgyz highlanders with high altitude pulmonary hypertension (n=36) suggest that the time in wakefulness after sleep onset was increased and NREM sleep stages 1 and 2 were increased in comparison to healthy highlanders (n=54) and lowlanders (n=34) (22); highlanders with high altitude pulmonary hypertension had a significantly higher apnea/hypopnea index compared to both healthy highlanders and lowlanders.
Conclusions

Our review of the scientific literature on sleep and its disturbances at altitude confirm the longstanding notion that mountain tourists commonly perceive sleep disturbances with insomnia and frequent awakenings in the first few nights at altitude. High altitude insomnia is generally modest and it may or may not be associated with acute mountain sickness. The most consistent change reported from the few well designed polysomnographic studies performed in healthy lowlanders arriving at altitude is a decrease in slow wave sleep. This may not only affect subjective well-being but also impair memory consolidation during sleep and possibly vigilance, cognitive and visual-motor performance during daytime. However, the evidence to support these assumptions is still scant. Further studies are required to better quantify the effects of different levels of altitude on sleep in persons of both sexes and of various ages and to elucidate the underlying physiological mechanisms. Areas of uncertainty that should be addressed by future research relate to the interaction of high altitude periodic breathing and sleep fragmentation, to the role of hypoxia in impairing daytime performance directly or via sleep disturbance (sleep fragmentation and altered sleep structure), and to the changes in sleep with acclimatization. A better evaluation of the efficacy and safety of drugs for treatment of altitude related sleep disturbances is also required. The research on sleep in high altitude residents is still at its very beginning but might provide insights that are valuable for the better understanding and treatment of sleep disturbances in patients with chronic hypoxia at lowlands due to cardiac or pulmonary disease. In summary, although recent research has provided several facts that corroborate or refute previous guesses more research is clearly needed to advance our understanding of various aspects of sleep at altitude.
Figure Legends

Figure 1. Qualitative representation of sleep structure recorded at sea level and in the first night at altitude. The area encircled by the outer line reflects the time in bed, the area of the shaded inner pie chart the time asleep (41). Compared to sea level, sleep at higher altitude is characterized by a reduced sleep efficiency, i.e., the ratio of sleep time to the time in bed is decreased. The fractions of deep sleep non-rapid eye movement sleep (NR3&4) and of rapid eye movement sleep (REM) are reduced, the fractions superficial sleep stages (NR1&2) are prolonged. Some studies have also found an increased number of arousals at higher altitude which is reflected by the denser hatching in the right vs. the left panel (i.e., more frequent arousals at altitude >1500 m compared to sea level).

Figure 2. Data from a randomized trial evaluating effects of altitude on sleep and cognitive performance in 51 healthy men. The upper panels (A) show the decrease in nocturnal oxygen saturation and the increase in the apnea/hypopnea index at the higher altitudes (left side, 1630 m and 2590 m compared to 490 m), and the corresponding changes in deep sleep (on the right); the number of arousals is similar at the 3 altitudes († and †† = P<0.05 vs. 490 m and vs. 490 m and 1650 m, respectively). The middle panels (B) show spectral plots of power density from frontal (F3A2, left) and central electroencephalographic derivations (C3A2, right) that quantify the reduction in slow wave activity (0.8-4.6 Hz) and the increase in the spindle frequency range (10-15 Hz) at the higher altitudes (1630 m and 2590 m, nights 1 and 2, N1 and N2, compared to a night at 490 m). In the lowest panels (C) pre-sleep (left) and post-sleep (right) performance in a visual-motor task are illustrated. The decrement of overnight memory consolidation at 2590 m vs. 490 m is reflected in the increase in directional error in 264 movements at 2590 m vs. 490 m. Panels A-C are reproduced in modified form with permission from (24; 48; 51).
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Table 1. Systematic literature research on sleep at altitude assessed by polysomnography

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Table 2. Sleep in lowlanders ascending to altitude

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<td>51</td>
<td>Healthy men living below 800 m, age 24 y.</td>
<td><strong>Time at altitude</strong> 1 day at 490 m, 2 days at 1630 m, 2 days at 2590 m. <strong>Sleep</strong> Sleep efficiency, %: 490 m 97; 1630 m 1st night 98; 2nd night 99; 2590 m 1st night 98; 2nd night 98. NREM 3 and 4, %: 490 m 24; 1630 m 1st night 24; 2nd night 24; 2590 m 1st night 20*; 2nd night 21. REM, %: 490 m 19; 1630 m 1st night 22; 2nd night 26*; 2590 m 1st night 20; 2nd night 22*. Arousal index, 1/h: 490 m 8.3; 1630 m 1st night 6.5; 2nd night 6.8; 2590 m 1st night 7.7; 2nd night 7.7. <strong>Breathing</strong> ( SpO_2 ), %: 490 m 96; 1650 m 1st night 94*; 2nd night 94*; 2590 m 1st night 90*; 2nd night 91*. AHI, 1/h: 490 m 4.6; 1630 m 1st night 7.0*; 2nd night 5.4*; 2590 m 1st night 13.1*; 2nd night 8.0*.</td>
<td>Vigilance and cognitive performance during daytime tests did not show significant changes at altitude. However, slight impairments in postural control were noted (47).</td>
</tr>
<tr>
<td>Stadelmann et al. 2013 (48). Data collected during study by Latshang et al. 2013(24).</td>
<td>Design: Randomized cross-over. 1 day at 490 m, 2 days at 1630 m, 2 days at 2590 m. Setting: Field study. University</td>
<td>1b</td>
<td>44</td>
<td>Healthy men living below 800 m, age 24 y.</td>
<td><strong>Time at altitude</strong> 1 day at 490 m, 2 days at 1630 m, 2 days at 2590 m. <strong>Sleep, EEG, power spectral analysis</strong> Central (C3A2) slow wave activity (0.8-4.6 Hz), compared to 490 m. % change: 1630 m 1st night -16; 2nd night -13; 2590 m 1st night -15; 2nd night -14.</td>
<td>Quantitative spectral analysis of frontal and central EEG derivations revealed an altitude dependent decrease in slow wave activity. In addition, there was a slight but statistically significant increase in the</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Number</td>
<td>Participants</td>
<td>Setting</td>
<td>Time at altitude</td>
<td>Sleep, EEG, power spectral analysis</td>
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<tr>
<td>Stadelmann et al. 2014 (49). Data collected during study by Latshang et al. 2013 (24).</td>
<td>Randomized cross-over.</td>
<td>1b 20</td>
<td>Healthy men living below 800 m; age 24 y. Subset of participants in study by Latshang et al. (24).</td>
<td>Data suggest that visual scoring of EEG arousals according to conventional criteria may miss subtle EEG changes at altitude.</td>
<td>1 day at 490 m, 2 days at 1630 m, 2 days at 2590 m.</td>
<td>Comparison of EEG power spectral density during epochs containing periodic breathing without arousals and periods with normal breathing but arousals reveal similar qualitative changes. Breathing See (24).</td>
</tr>
<tr>
<td>Tseng et al., 2014 (52).</td>
<td>Observational.</td>
<td>4 40</td>
<td>Healthy subjects, 14 men, age 39.9 y.</td>
<td></td>
<td>9 m (before and after altitude exposure: T0 and T3), and at 3150 m, day 1 and 2: T1 and T2).</td>
<td>Sleep efficieney, %: 9 m T0 and T3 86 and 87; 3150 m T1 and T2 82* and 84. NREM 3 and 4, %: 9 m T0 and T3 7 and 9; 3150 m T1 and T2 7* and 7*. REM, %: 9 m T0 and T3 7 and 16; 3150 m T1 and T2 14 and 7. T0 15. Subjects with acute mountain sickness: REM, %, at 3150 m, T1 and T2 10.9, 12.1 vs. 16.5 and 16.9 in subjects without acute mountain sickness (P&lt;0.05 both instances). Arousal index, 1/h: 9 m T0 and T3 20.7 and 21.9; 3150 m</td>
</tr>
</tbody>
</table>
Bloch KE et al., Sleep at altitude

T1 and T2 24.2* and 26.2*.

**Breathing**

SpO₂, %: 9 m T0 and T3 97 and 97; 3150 m T1 and T2 81* and 83*.

AH1 1/h: 9 m T0 and T3 0.8 and 1.2; 3150 m T1 and T2 7.4* and 3.5*.

* P<0.05 vs. 9 m

**Nussbaumer-Ochsner at al. 2012 (39)**

<table>
<thead>
<tr>
<th>Design</th>
<th>4</th>
<th>16 Healthy mountaineers, age 45 y.</th>
<th>Time at altitude</th>
<th>1 day at 490 m, 3 days at 4559 m.</th>
<th>Symptoms of AMS and of disturbed sleep were significantly reduced in the morning after the 3rd vs. the 1st night at 4559 m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting</td>
<td></td>
<td>Field study. Sleep laboratory in Zurich, Regina Margherita hut at 4559 m, Swiss/Italian Alps.</td>
<td>Sleep</td>
<td>Sleep efficiency, %: 490 m 93; 4559 m night 1 69*; night 3 75.</td>
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<td></td>
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<td>Stage 3 and 4, %: 490 m 18; 4559 m night 1 6; night 3 11¶.</td>
<td>REM, %: 490 m 8; 4559 m night 1 3*; night 2 4¶.</td>
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<td></td>
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<td>Arousal index, 1/h: 490 m 5.4; 4559 m night 1 17.9*; night 3 5.7¶.</td>
<td><strong>Breathing</strong></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td>SpO₂: 490 m 96; 4559 m night 1 67*, night 3 71*.</td>
<td>AH1 1/h: 490 m 0.1; 4559 m night 1 60.9*; night 3 86.5*¶.</td>
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<td>* P&lt;0.05 vs. 490 m; ¶ P&lt;0.05 vs. day 1 at same altitude</td>
<td>Objective and subjective measurements of sleep quantity and quality did not change significantly with changes in simulated altitude, nor did post-sleep neurobehavioral performance or mood.</td>
<td></td>
</tr>
</tbody>
</table>

**Muhm et al., 2009 (30).**

<table>
<thead>
<tr>
<th>Design</th>
<th>1b</th>
<th>20 Healthy men, age 44.1 y.</th>
<th>Time at altitude</th>
<th>18 h at 305 m and at 2438 m, respectively.</th>
<th>Objective and subjective measurements of sleep quantity and quality did not change significantly with changes in simulated altitude, nor did post-sleep neurobehavioral performance or mood.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting</td>
<td></td>
<td></td>
<td>Sleep</td>
<td>Sleep efficiency, %: 305 m 87; 2438 m 84.</td>
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<tr>
<td></td>
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<td>Slow wave sleep, %: 305 m 3; 2438 m 2.</td>
<td>REM, %: 305 m 17; 2438 m 17.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Arousal index, 1/h: 305 m 13.9; 2438 m 15.2.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hypobaric chamber simulating 305 m and 2438 m.

**SpO₂, %:** 305 m 92; 2438 m 86.

**Breathing**

SpO₂: 305 m 92; 2438 m 86*.

Oxygen desaturation index (>3%), 1/h: 305 m 3; 2438 m 12*.

* P<0.05 vs. 305 m

---

**Design**

Randomized, placebo-controlled, cross-over.

Sleep studies during 4 nights, separated by 1 week wash-out in normobaric conditions.

Treatment with zolpidem 10 mg, zaleplon 10 mg, placebo at simulated 4000 m, respectively.

**Setting**

Hypobaric chamber simulating 80 m and 4000 m.

---

**Beaumont et al., 2004 (3).**

**Time at altitude**

1 night at 80 m, 3 nights at simulated 4000 m.

**Sleep**

Sleep efficiency, %: 80 m 87; 4000 m: placebo 81; zaleplon 84; zolpidem 85.

NREM 3 and 4, %: 80 m 23; 4000 m: placebo 18*; zaleplon 20; zolpidem 24¶.

REM %: 80 m 17; 4000 m: placebo 7*; zaleplon 10*; zolpidem 10*.

Arousal index, 1/h: NA.

**Breathing**

SpO₂, %: 0 m 98; 4000 m: placebo 71*; zaleplon 71*; ALT zolpidem 71*.

AHI, 1/h: 80 m 0.0; 4000 m: placebo 82.9*, zaleplon 80.2*, zolpidem 73.6*.

* P<0.05 vs. 80 m; ¶ P<0.05 vs. placebo

---

**Beaumont et al., 2007 (4).**

**Time at altitude**

1 night a 1000 m, 3 periods of 3 consecutive nights at 3613 m, 1 night on placebo, 1 night on zolpidem, 1 night on zaleplon.

**Sleep**

Altitude exposure was associated with a significant reduction in NREM sleep stage 4 and in sleep efficiency, and this was partially reversed with
of nights at 3613 m with washout phase.

**Setting**
Field study. Military School of High Mountain, Chamonix, France and Cosmiques hut in the French Alps. Nights 1-3 to test zolpidem 10 mg, zaleplon 10 mg, placebo. Washout phase of at least 1 week between treatment nights.

**Sleep**
Sleep efficiency %: 1000 m 94; 3613 m: placebo 91*; zaleplon 93¶; zolpidem 93¶. Arousals, 1/h: NA.
NREM 4 (SWS NA), %: 1000 m 18; 3613 m: placebo 12*; zaleplon 13; zolpidem 15¶.
REM %: 1000 m 18; 3613 m: placebo 19; zaleplon 19; zolpidem 17.

**Breathing**
SpO₂, %: 1000 m 96; 3613 m: placebo 83*; zaleplon 84*; zolpidem 82*.

* P<0.05 vs. 1000 m; ¶ P<0.05 vs. placebo

---

**Design**
Randomized cross-over. 1 day at 490 m, 2 days at 1860 m, 2 days at 2590 m.
Discontinuation of CPAP therapy during study.

**Setting**
Field study. University Hospital Zurich, mountain hostels in Swiss Alps.

**Patients with obstructive sleep apnea**

<table>
<thead>
<tr>
<th>Time at altitude</th>
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<tr>
<td>1 day at 490 m, 2 days at 1860 m, 2 days at 2590 m.</td>
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</tbody>
</table>

**Sleep**
Sleep efficiency, %: 490 m 86; 1860m 1st night 82; 2nd night 79*; 2590 m 1st night 78*; 2nd night 71*.
NREM 3 and 4, %: 490 m 14; 1860m 1st night 12; 2nd night 14; 2590 m 1st night 6*; 2nd night 9*.
REM, %: 490 m 13; 1860m 1st night 13; 2nd night 13; 2590 m 1st night 10; 2nd night 10.
Arousal index, 1/h: 490 m 35.5; 1860m 1st night 41.8*; 2nd night 45.5*; 2590 m 1st night 51.3*; 2nd night 49.3*.

**Breathing**
SpO₂, %: 490 m 94; 1860m 1st night 90*; 2nd night 90*; 2590 m 1st night 86*; 2nd night 87*.
Bloch KE et al., Sleep at altitude

AHI, 1/h: 490 m 51.2; 1860m 1st night 85.1*; 2nd night 68.5*; 2590 m 1st night 90.0*; 2nd night 88.6*¶.

* P<0.05 vs. 490 m; P=NS night 2 vs. 1 at same altitude

| Design                  | 1b  | 18 Patients with obstructive sleep apnea syndrome living at <600 m, age 64 y. Discontinued their CPAP therapy during study. 1 day at 490 m, 2 days at 1860 m, 1 day at 2590 m. | Time at altitude | Sleep | Breathing |
|-------------------------|-----|-------------------------------------------------|----------------------|--------|
| Data collected during study of Nussbaumer-Ochsner et al. 2012 (35). | Randomized, placebo-controlled, double-blind cross-over. Acetazolamide 2x250 mg/d during stay at altitude vs. placebo. Discontinuation of CPAP therapy during study. 1 day at 490 m, 2 days at 1860 m, 1 day at 2590 m. | 1 day at 490 m, 2 days at 1860 m, 1 day at 2590 m. Outcomes assessed at 490 m off CPAP and at 2590 m 1st night on placebo and acetazolamide, respectively. | See (35) | SpO2, %: 490 m 93; 2590 m placebo 86*, acetazolamide 89*¶. Cerebral tissue oxygenation: 490 m 65; 2590 m placebo 59*, acetazolamide 61*¶. AHI, 1/h: 490 m 57.3; 2590 m placebo 86.5*, acetazolamide 67.4*¶. * P<0.05 vs. 490 m; ¶ P<0.05 vs. placebo at same altitude |
| Setting                 | Field study. University Hospital Zurich, mountain hostels in Swiss Alps. | Study using transcranial near-infrared spectroscopy during sleep. In patients with obstructive sleep apnea discontinuing their CPAP therapy during a stay at 2590 m (on placebo), nocturnal cerebral and arterial oxygenation were reduced in association with exacerbated sleep apnea. |

EBM = Oxford Center of Evidence-based Medicine Level of Evidence: level 1b = individual randomized, controlled trial, level 4= case series; N = number of participants. Numbers in the participants and results columns are means or medians. CPAP = continuous positive airway pressure; AHI = apnea/hypopnea index, REM = rapid eye movement sleep, NREM non-rapid eye movement sleep.
### Table 3. Sleep in lowlanders ascending to altitude, effect of acclimatization

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design &amp; Setting</th>
<th>EBM</th>
<th>N</th>
<th>Participants</th>
<th>Main results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latshang et al., 2013 (24). See also Table S2.</td>
<td><strong>Design</strong></td>
<td>1b</td>
<td>51</td>
<td>Healthy men living below 800 m, age 24 y.</td>
<td><strong>Time at altitude</strong></td>
<td>Acclimatization (days at altitude) was a significant independent predictor of the % NREM sleep stages 3 and 4, of the % time with wakefulness after sleep onset, and of the AHI when controlling for several covariables.</td>
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<tr>
<td></td>
<td>Randomized cross-over altitude exposure 1 day at 490 m, 2 days at 1630 m, 2 days at 2590 m.</td>
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<td><strong>Sleep</strong></td>
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<td></td>
<td><strong>Setting</strong></td>
<td></td>
<td></td>
<td></td>
<td>Sleep efficiency, %: 490 m 97; 1630 m 1st night 98; 2nd night 99; 2590 m 1st night 98; 2nd night 98.</td>
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<td></td>
<td>Field study. University Hospital Zurich, mountain hostels in Swiss Alps.</td>
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<td></td>
<td>NREM 3 and 4, %: 490 m 24; 1630 m 1st night 24; 2nd night 24; 2590 m 1st night 20*; 2nd night 21.</td>
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<td>REM, %: 490 m 19; 1630 m 1st night 22; 2nd night 26*¶; 2590 m 1st night 20; 2nd night 22.</td>
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<td>Arousal index, 1/h: 490 m 8.3; 1630 m 1st night 6.5; 2nd night 6.8; 2590 m 1st night 7.7; 2nd night 7.7.</td>
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<td><strong>Breathing</strong></td>
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<td>SpO2, %: 490 m 96; 1650 m 1st night 94*; 2nd night 94*; 2590 m 1st night 90*; 2nd night 91*¶.</td>
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<td>AHI, 1/h: 490 m 4.6; 1630 m 1st night 7.0*; 2nd night 5.4*; 2590 m 1st night 13.1*; 2nd night 8.0*¶.</td>
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<td>* P&lt;0.05 vs. 490 m; ¶ P&lt;0.05 vs. day 1 at same altitude</td>
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<tr>
<td>Stadelmann et al. 2013(48). See also Table S2. Data collected during study by Latshang et al.</td>
<td><strong>Design</strong></td>
<td>1b</td>
<td>44</td>
<td>Healthy men living below 800 m, age 24 y.</td>
<td><strong>Time at altitude</strong></td>
<td>Quantitative spectral analysis of frontal and central EEG derivations revealed that the altitude dependent decreased in slow wave activity was more pronounced in the first compared to the second night at</td>
</tr>
<tr>
<td></td>
<td>Randomized cross-over altitude exposure 1 day at 490 m, 2 days at 1630 m, 2 days at 2590 m.</td>
<td></td>
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<td></td>
<td><strong>Sleep, EEG, power spectral analysis</strong></td>
<td></td>
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<tr>
<td></td>
<td><strong>Setting</strong></td>
<td></td>
<td></td>
<td></td>
<td>Central (C3A2) slow wave activity (0.8-4.6 Hz), compared to 490 m, % change: 1630 m 1st night -16; 2nd night -13; 2590 m 1st night -15; 2nd night -14.</td>
<td></td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Setting</td>
<td>Time at altitude</td>
<td>Sleep</td>
<td>Breathing</td>
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<tr>
<td>Tseng et al., 2014</td>
<td>Observational.</td>
<td>Field study. Studies at Taipei and at Mountain Ho-Huan, Taiwan.</td>
<td>9 m (before and after altitude exposure: T0 and T3), and at 3150 m, day 1 and 2: T1 and T2.</td>
<td>Sleep efficiency, %: 9 m T0 and T3 86 and 87; 3150 m T1 and T2 82* and 84. NREM 3 and 4, %: 9 m T0 and T3 7 and 9; 3150 m T1 and T2 7* and 7*. REM, %: 9 m T0 and T3 7 and 16; 3150 m T1 and T2 14 and 7.T0 15. Arousal index, 1/h: 9 m T0 and T3 20.7 and 21.9; 3150 m T1 and T2 24.2* and 26.2*.</td>
<td>SpO2, %: 9 m T0 and T3 97 and 97; 3150 m T1 and T2 81* and 83*. AH1 1/h: 9 m T0 and T3 0.8 and 1.2; 3150 m T1 and T2 7.4* and 3.5*.</td>
<td></td>
</tr>
<tr>
<td>Nussbaumer-Ochsner et al. 2012 (39).</td>
<td>Observational.</td>
<td>1 day at 490 m, 3 days at 4559 m.</td>
<td>Symptoms of AMS and of disturbed sleep were significantly reduced in the morning after the 3rd day.</td>
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<tr>
<td>Nussbaumer-Ochsner et al. 2010 (37).</td>
<td><strong>Design</strong></td>
<td><strong>1</strong>b</td>
<td><strong>34</strong> Patients with obstructive sleep apnea syndrome living at &lt;600 m, age 62 y. Discontinued their CPAP therapy during the study.</td>
<td><strong>Time at altitude</strong></td>
<td>Patients with obstructive sleep apnea syndrome discontinuing their CPAP therapy experience pronounced hypoxemia and exacerbation of sleep apnea during a stay at moderate altitude. There was no difference in sleep characteristics between the first and second night at the two altitudes.</td>
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<tr>
<td>Randomized cross-over. 1 day at 490 m, 2 days at 1860 m, 2 days at 2590 m. Discontinuation of CPAP therapy during study.</td>
<td><strong>Setting</strong></td>
<td><strong>Field study. University Hospital Zurich, mountain hostels in Swiss Alps.</strong></td>
<td><strong>Sleep</strong></td>
<td>1 day at 490 m, 2 days at 1860 m, 2 days at 2590 m.</td>
<td><strong>Breathing</strong></td>
<td></td>
</tr>
<tr>
<td>See also Table S2.</td>
<td></td>
<td></td>
<td>Sleep efficiency, %: 490 m 86; 1860 m 1st night 82; 2nd night 79*; 2590 m 1st night 78*; 2nd night 71*. NREM 3 and 4, %: 490 m 14; 1860 m 1st night 12; 2nd night 14; 2590 m 1st night 6*; 2nd night 9*. REM, %: 490 m 13; 1860 m 1st night 13; 2nd night 13; 2590 m 1st night 10; 2nd night 10.</td>
<td>Arousal index, 1/h: 490 m 35.5; 1860 m 1st night 41.8*; 2nd night 45.5*; 2590 m 1st night 51.3*; 2nd night 49.3*.</td>
<td>SpO$_2$, %: 490 m 94; 1860 m 1st night 90*; 2nd night 90*; 2590 m 1st night 86*; 2nd night 87*. AHI 1/h: 490 m 51.2; 1860 m 1st night 85.1*; 2nd night 68.5*; 2590 m 1st night 90.0*; 2nd night 88.6*¶.</td>
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<tr>
<td>and 3 at 4559 m.</td>
<td><strong>Setting</strong></td>
<td>Field study. Sleep laboratory in Zurich, Regina Margherita hut at 4559 m, Swiss/Italian Alps.</td>
<td>Stage 3 and 4, %: 490 m 18; 4559 m night 1 16; night 3 11¶. REM, %: 490 m 8; 4559 m night 1 3*; night 2 4¶. Arousal index, 1/h: 490 m 5.4; 4559 m night 1 17.9*; night 3 5.7¶.</td>
<td></td>
<td>SpO$_2$: 490 m 96; 4559 m night 1 67*, night 3 71*. AHI 1/h: 490 m 0.1; 4559 m night 1 60.9*; night 3 86.5**¶.</td>
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<tr>
<td><strong>Sleep</strong></td>
<td><strong>Laboratory</strong></td>
<td><strong>Sleep</strong></td>
<td>Sleep efficiency, %: 490 m 93; 4559 m night 1 69*; night 3 75.</td>
<td></td>
<td>* P&lt;0.05 vs. 490 m; ¶ P&lt;0.05 vs. day 1 at same altitude</td>
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</tbody>
</table>

* P<0.05 vs. 490 m; P=NS night 2 vs. 1 at same altitude.
EBM = Oxford Center of Evidence-based Medicine Level of Evidence: level 1b = individual randomized, controlled trial, level 4 = case series;
N = number of participants. Numbers in the participants and results columns are means or medians.
CPAP = continuous positive airway pressure; AHI = apnea/hypopnea index, REM = rapid eye movement sleep, NREM non-rapid eye movement sleep
Table 4. Treatment of sleep disturbances at altitude

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design &amp; Setting</th>
<th>EBM</th>
<th>N</th>
<th>Participants</th>
<th>Main results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beaumont et al., 2004</td>
<td>Design</td>
<td>4</td>
<td>12</td>
<td>Healthy men, age 29.9 y.</td>
<td><strong>Time at altitude</strong></td>
<td>Minor effect of hypobaric hypoxia on slow wave and REM sleep.</td>
</tr>
<tr>
<td></td>
<td>Randomized, placebo-controlled, cross-over. Sleep studies during 4 nights, separated by 1 week wash-out in normobaric conditions. Treatment with zolpidem 10 mg, zaleplon 10 mg, placebo at simulated 4000 m, respectively.</td>
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<td>Accordingly, the effect of drugs was also minor. The drugs did not induce any significant changes in oxygen saturation or periodic breathing.</td>
</tr>
<tr>
<td></td>
<td>Setting</td>
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<tr>
<td></td>
<td>Hypobaric chamber simulating 80 m and 4000 m.</td>
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<tr>
<td>Beaumont et al., 2007</td>
<td>Design</td>
<td>4</td>
<td>12</td>
<td>Healthy military trainees, age 22.2 y.</td>
<td><strong>Time at altitude</strong></td>
<td>Altitude exposure was associated with a significant reduction in NREM sleep stage 4 and in sleep efficiency, and this was partially reversed with zolpidem. Nocturnal</td>
</tr>
<tr>
<td></td>
<td>Randomized, placebo-controlled cross-over. 5 days at 1000 m, 3 periods of nights at 3613 m with washout</td>
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<td>Sleep efficiency, %: 80 m 87; 4000 m: placebo 81; zaleplon 84; zolpidem 85. NREM 3 and 4, %: 80 m 23; 4000 m: placebo 18*; zaleplon 20; zolpidem 24¶. REM %: 80 m 17; 4000 m: placebo 7*; zaleplon 10*; zolpidem 10*. Arousal index, 1/h: NA. Breathing SpO2, %: 0 m 98; 4000 m: placebo 71*; zaleplon 71*; ALT zolpidem 71*. AHI, 1/h: 80 m 0.0; 4000 m: placebo 82.9*, zaleplon 80.2*, zolpidem 73.6*.</td>
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</tbody>
</table>
Bloch KE et al., Sleep at altitude

<table>
<thead>
<tr>
<th>Setting</th>
<th>Effect of zolpidem, zaleplon vs. placebo on sleep at altitude.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field study. Military School of High Mountain, Chamonix, France and Cosmiques hut in the French Alps. Nights 1-3 to test zolpidem 10 mg, zaleplon 10 mg, placebo. Washout phase of at least 1 week between treatment nights.</td>
<td>Sleep efficiency %: 1000 m 94; 3613 m: placebo 91*; zaleplon 93¶; zolpidem 93¶. Arousal, 1/h: NA. NREM 4 (SWS NA), %: 1000 m 18; 3613 m: placebo 12*; zaleplon 13; zolpidem 15¶. REM %: 1000 m 18; 3613 m: placebo 19; zaleplon 19; zolpidem 17.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Breathing</th>
<th>SpO2 was not affected by either drug.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SpO2, %: 1000 m 96; 3613 m: placebo 83*; zaleplon 84*; zolpidem 82*.</td>
<td>* P&lt;0.05 vs. 1000 m; ¶ P&lt;0.05 vs. placebo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nussbaumer-Ochsner et al., 2011(38).</th>
<th>Design</th>
<th>36</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized study of dexamethasone prophylaxis of high altitude pulmonary edema. Subjects were randomized to receive dexamethasone 2x8 mg/d taken before ascent and during stay at altitude or to the same medication starting on day 2 at altitude only. Studies at 490 m and during night 1 and 3 at 4559 m.</td>
<td>High altitude pulmonary edema susceptibles but otherwise healthy subjects, age 47 y.</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Setting</th>
<th>Effect of dexamethasone on sleep at high altitude.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field study. Sleep laboratory in Zurich, Regina Margherita</td>
<td>Time at altitude 1 night at 490 m, 3 nights at 4559 m.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dexamethasone late group: Sleep</th>
<th>SpO2 was not affected by either drug.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep efficiency, %: 490 m 91; 4559 m night 1 65*; night 3 69*.</td>
<td>* P&lt;0.05 vs. 490 m; ¶ P&lt;0.05 vs. placebo</td>
</tr>
<tr>
<td>Stage 3 and 4, %: 490 m 22; 4559 m night 1 11*; night 3 20#.</td>
<td></td>
</tr>
<tr>
<td>REM, %: 490 m 6; 4559 m night 1 2*; night 3 2*.</td>
<td></td>
</tr>
<tr>
<td>Arousal index, 1/h: 490 m 3.0; 4559 m night 1 8.1*; night 3 6.0.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Breathing</th>
<th>SpO2, %: 490 m 96; 4459 m night 1 71*; night 3 80%#.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI, 1/h: 490 m 1.9; 4459 m night 1 91.3*.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time at altitude</th>
<th>1 night at 490 m, 3 nights at 4559 m.</th>
</tr>
</thead>
</table>

Multiple regression analysis controlling for the differences in the nocturnal SpO2 and the AHI suggested an independent effect of dexamethasone in improving sleep efficiency at 4559 m. The independent effects of dexamethasone on slow wave sleep and on the arousal index were non-significant.
Sleep at altitude hut at 4559 m, Swiss/Italian Alps.

Dexamethasone early group:
Sleep
Sleep efficiency, %: 490 m 96; 4559 m night 1 95*; night 3 90*¶.
Stage 3 and 4, %: 490 m 19; 4559 m night 1 9*; night 3 8*¶.
REM, %: 490 m 10; 4559 m night 1 1*; night 2 2*.
Arousal index, 1/h: 490 m 2.0; 4559 m night 1 5.6*; night 3 6.2*.

Breathing
SpO2, %: 490 m 95; 4459 m night 1 78*; night 3 79*.
AHI, 1/h: 490 m 1.7; 4459 m night 1 85.3*; night 3 52.3*#.

* P<0.05 vs. 490 m; ¶ P<0.05 vs. Dexamethasone early; # P<0.05 vs. day 1 at 4559 m.

Nussbaumer-Ochsner et al. 2012 (35).

Design
Randomized, placebo-controlled, double-blind cross-over. Acetazolamide 2x250 mg/d during stay at altitude vs. placebo. Discontinuation of CPAP therapy during study.
1 day at 490 m, 2 days at 1860 m, 1 day at 2590 m. Outcomes assessed at 490 m, 1860 m 2nd night and 2590 m 1st night on placebo and acetazolamide, respectively.

Time at altitude
1 day at 490 m, 2 days at 1860 m, 1 day at 2590 m. Outcomes assessed at 490 m, 1860 m 2nd night and 2590 m 1st night on placebo and acetazolamide, respectively.

Sleep
Sleep efficiency, %: 490 m 78; 1860 m, placebo 72, acetazolamide 81*¶; 2590 m In patients with obstructive sleep apnea syndrome discontinuing their CPAP therapy during a stay at 1680 m and 2590 m acetazolamide 2x250 mg/d was superior to placebo in terms of nocturnal oxygen saturation, AHI, sleep efficiency, and arousal index. In addition,
Bloch KE et al., Sleep at altitude

m, 1 day at 2590 m.

Setting
Field study. University Hospital Zurich, mountain hostels in Swiss Alps.

Placebo 66*; acetazolamide 77¶.
NREM 3 and 4, %: 490 m 6; 1860 m placebo 6, acetazolamide 8; 2590 m placebo 4*, acetazolamide 3*.
REM, %: 490 m 8; 1860m placebo 12, acetazolamide 8; 2590 m placebo 9, acetazolamide 8.
Arousal index, 1/h: 490 m 44.9; 1860m placebo 52.8, acetazolamide 47.4; 2590 m placebo 72.7*¶, acetazolamide 54.9*¶.

Breathing
SpO2, %: 490 m 93; 1860 m placebo 89*¶, acetazolamide 91*; 2590 m placebo 85*, acetazolamide 88*¶.
AHI, 1/h: 490 m 51.2; 1860 m placebo 63.6*, acetazolamide 48.0¶; 2590 m placebo 86.2*, acetazolamide 61.4*¶.
* P<0.05 vs. 490 m; ¶ P<0.05 vs. placebo at same altitude

Ulrich et al. 2014 (53).

Data collected during study of Nussbaumer-Ochsner et al. 2012 (35).

Design
Randomized, placebo-controlled, double-blind crossover. Acetazolamide 2x250 mg/d during stay at altitude vs. placebo. Discontinuation of CPAP therapy during study. 1 day at 490 m, 2 days at 1860 m, 1 day at 2590 m.

Time at altitude
1 day at 490 m, 2 days at 1860 m, 1 day at 2590 m. Outcomes assessed at 490 m off CPAP and at 2590 m 1st night on placebo and acetazolamide, respectively.

Sleep
See (35)

Breathing
Study using transcranial near-infrared spectroscopy during sleep.

In patients with obstructive sleep apnea staying at 2590 m, nocturnal cerebral and arterial oxygenation were reduced in association with exacerbated sleep apnea.

Acetazolamide improved cerebral tissue oxygenation at altitude compared to placebo (Ulrich et al. 2014 (53)). Therefore, patients with obstructive sleep apnea may benefit from acetazolamide therapy during a stay at altitude if CPAP therapy is not feasible.

acetazolamide improved cerebral tissue oxygenation at altitude compared to placebo (Ulrich et al. 2014 (53)). Therefore, patients with obstructive sleep apnea may benefit from acetazolamide therapy during a stay at altitude if CPAP therapy is not feasible.
Bloch KE et al., Sleep at altitude

m, 1 day at 2590 m.

Setting
Field study. University Hospital Zurich, mountain hostels in Swiss Alps.

SpO₂, %: 490 m 93; 2590 m placebo 86*, acetazolamide 89**.
Cerebral tissue oxygenation: 490 m 65; 2590 m placebo 59*, acetazolamide 61**.
AHI, 1/h: 490 m 57.3; 2590 m placebo 86.5*, acetazolamide 67.4**.
* P<0.05 vs. 490 m; ¶ P<0.05 vs. placebo at same altitude.

Improved cerebral tissue oxygenation, arterial oxygen saturation and the AHI without impairing the cerebral blood flow response to apneas.

Latshang et al. 2012 (25).

Design
Randomized, placebo-controlled, double-blind cross-over. Acetazolamide 250 mg in the morning and x500mg/d in the evening during stay at altitude vs. placebo. CPAP therapy during stay at altitude.

1 day at 490 m, 2 days at 1860 m, 1 day at 2590 m.

Setting
Field study. University Hospital Zurich, mountain hostels in Swiss Alps.

51 Patients with obstructive sleep apnea syndrome living at <600 m, age 63 y.

Time at altitude
2 days at 490 m, 2 days at 1860 m, 1 day at 2590 m.
Outcomes assessed at 490 m with and without CPAP therapy, and at 1860 m 2nd night and 2590 m 1st night on placebo and acetazolamide, respectively.

Sleep
Sleep efficiency, %: 490 m CPAP 80; 1860 m, CPAP + placebo 81, CPAP + acetazolamide 87**, 2590 m CPAP + placebo 79; CPAP + acetazolamide 85**.
NREM 3 and 4, %: 490 m CPAP 15; 1860 m CPAP + placebo 13, CPAP + acetazolamide 15; 2590 m CPAP + placebo 10*, CPAP + acetazolamide 13**.
REM, %: 490 m CPAP; 1860m CPAP + placebo 12, CPAP + acetazolamide 8; 2590 m CPAP + placebo 9, CPAP +

In patients with obstructive sleep apnea syndrome spending 3 days at 1650 m and 2590 m, a combined treatment with acetazolamide and CPAP therapy with computer controlled mask pressure adjustments improved nocturnal oxygen saturation, the AHI and some aspects of sleep structure in comparison to CPAP therapy and placebo. Therefore, patients with obstructive sleep apnea should be recommended to continue using their CPAP therapy during an altitude sojourn and they may benefit
<table>
<thead>
<tr>
<th>Altitude (m)</th>
<th>Treatment</th>
<th>Arousal Index (1/h)</th>
<th>Breathing</th>
</tr>
</thead>
<tbody>
<tr>
<td>490</td>
<td>CPAP</td>
<td>52.8</td>
<td>SpO2 (%): 93*</td>
</tr>
<tr>
<td></td>
<td>acetazolamide</td>
<td>47.4</td>
<td>93*¶</td>
</tr>
<tr>
<td>1860</td>
<td>CPAP + placebo</td>
<td>52.8</td>
<td>93*¶</td>
</tr>
<tr>
<td></td>
<td>CPAP + acetazolamide</td>
<td>47.4</td>
<td>93*¶</td>
</tr>
<tr>
<td></td>
<td>2590 m CPAP + placebo</td>
<td>72.7</td>
<td>89*</td>
</tr>
<tr>
<td></td>
<td>CPAP + acetazolamide</td>
<td>54.9</td>
<td>91*¶</td>
</tr>
</tbody>
</table>

AHI, 1/h: 490 m off-CPAP 58.3*, CPAP 6.6; 1860 m CPAP + placebo 10.7*, CPAP + acetazolamide 5.8*¶; 2590 m CPAP + placebo 19.3*, CPAP + acetazolamide 6.8*¶.

* P<0.05 vs. 490 m on CPAP; ¶ P<0.05 vs. CPAP + placebo at same altitude from additional treatment with acetazolamide.

EBM = Oxford Center of Evidence-based Medicine Level of Evidence: level 1b = individual randomized, controlled trial, level 3b = individual case-control study, level 4 = case series; N = number of participants. Numbers in the participants and results columns are means or medians.

CPAP = continuous positive airway pressure; AHI = apnea/hypopnea index, REM = rapid eye movement sleep, NREM non-rapid eye movement sleep