# Medication Effects on Sleep and Breathing

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**KEYWORDS**

• Obstructive sleep apnea • Central sleep apnea • Hypnotics • Benzodiazepines • Antipsychotics • Estrogen • Progesterone • Testosterone

**KEY POINTS**

- Benzodiazepines are generally safe in low doses but in higher doses and in select patients they may be associated with respiratory depression, hypoventilation, hypoxemia, and obstructive sleep apnea (OSA).
- Narcotics can be associated with apneas and hypoventilation with increased risk with higher doses and use of other central nervous system depressants.
- Nonbenzodiazepine hypnotics, acetazolamide, and theophylline promote stable respirations at high altitude.
- Antidepressants may partially improve OSA by suppressing stage rapid eye movement and increasing upper airway tone but do not completely treat OSA.
- Hormonal therapy may effect sleep-disordered breathing and hypoventilation.
- Nasal steroids and leukotriene antagonists improve OSA by improving nasal airway resistance.

## INTRODUCTION

Respiration during sleep is regulated by circadian, endocrine, mechanical, and chemical factors. The volitional control of breathing during wakefulness is abolished during sleep and the hypercapnic threshold is increased.[1] Furthermore, the diminished hypoxic and hypercapnic ventilatory responses are more pronounced in rapid eye movement (REM) sleep compared with non-REM (NREM) sleep.[2] Sleep stage also affects the respiratory pattern. Periodic breathing can be observed in stages N1 or N2 of NREM sleep. In contrast, respiration is stable and regular during stage N3 sleep.[3] Stage REM is characterized by an irregular respiratory pattern. Additionally, REM-associated atonia in which the diaphragm remains the sole primary muscle of respiration may be associated with severe respiratory events.[4] Tidal volume and minute ventilation decrease during sleep and functional residual capacity is reduced.[5] Finally, upper airway (UA) dilator muscle tone decreases during sleep; this may increase the risk of sleep-disordered breathing (SDB).[6]

Medications can alter respiration during sleep through a variety of mechanisms. During sleep, medications can suppress the chemical or neural control of respiration resulting in central or obstructive apneas, hypopneas, hypoxemia, or hypoventilation. Medications can also alter sleep architecture by decreasing arousals, reducing the distribution of stage REM, or increasing the

Disclosure: No conflicts of interest to declare.
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Clin Chest Med 35 (2014) 557–569
http://dx.doi.org/10.1016/j.ccm.2014.06.011
0272-5231/14/$ – see front matter Published by Elsevier Inc.

duration of N2 or N3 sleep stages with secondary consequences on respiratory patterns. Medications can also improve respiration during sleep by functioning as respiratory stimulants or by increasing UA tone. Patient factors such as obesity, medical disorder such as chronic obstructive pulmonary disease (COPD) or asthma, psychiatric disorders, sleep disorders, and concomitant medication use can also influence a specific-agent effect on breathing during sleep.

## SEDATIVE HYPNOTIC AGENTS

### *Benzodiazepines*

Gamma-amino butyric acid (GABA) is the principle inhibitory neurotransmitter in the central nervous system (CNS). Benzodiazepines are widely used hypnotics and bind nonselectively to the pentameric $GABA_A$ receptor resulting in CNS inhibition.[7] Benzodiazepine hypnotics differ in duration of action, absorption, and potency. As a class, they reduce sleep latency (SOL), increase total sleep time (TST), decrease wake after sleep onset (WASO), and improve sleep quality. They increase N2 sleep and suppress N3 sleep. They increase REM latency and increase the number of spindles known as pseudospindles.[8]

Benzodiazepines can affect respiration during sleep through their sedative effects, suppression of arousals, and myorelaxation properties, or by increasing N2 sleep. Although considered respiratory depressants, they are generally safe in low doses. Stege and colleagues[9] investigated breathing and gas exchange during sleep in subjects with severe COPD but no baseline hypercapnia. Compared with placebo, temazepam was not associated with worsening hypoxemia, hypercapnia, or apnea-hypopnea index (AHI). A limitation of the study was the low doses of temazepam tested. Triazolam, a short-acting hypnotic, was also shown to have no adverse effects on respiration in subjects with COPD.[10] However, in another trial of subjects with mild-to-moderate OSA, temazepam (10 mg) was associated with greater respiratory impairment in subjects with a higher chemosensitivity in wakefulness.[11] Hypoxemia worsened during sleep but SDB did not.

Benzodiazepines can improve periodic breathing that develops at high altitude. These agents reduce wakefulness and augment stage N3 during the period of acclimatization after ascent. Dubowitz[12] studied the effects of temazepam 10 mg at 5300 m after acclimatization. Subjects taking temazepam versus placebo had fewer arousals, reduced periodic breathing, and a decreased frequency and severity of nocturnal oxygen desaturation. In another high-altitude study, temazepam reduced periodic breathing but was associated with a small decrease in mean nocturnal oxygen saturation ($SaO_2$).[13]

Other investigators have demonstrated that benzodiazepine administration resulted in adverse effects during early ascent to high altitude. Röggla and colleagues[14] performed a crossover trial comparing temazepam (10 mg) and placebo in 7 healthy men at 171 m and 3000 m. Measuring arterial blood gas at the two different elevations, they noted that temazepam use increased hypoxemia and hypercapnia at the moderate altitude.

Benzodiazepines can worsen SDB, hypoventilation, hypoxemia, and hypercapnia, and can increase UA collapsibility during sleep. Elderly patients taking higher doses of benzodiazepines, patients using agents with longer half-lives or agents with active metabolites, patients with underlying lung disease such as COPD, and those concomitantly using other sedative medications or substances such as narcotics or alcohol are more susceptible to adverse effects.[15] Flurazepam has been associated with increased apnea frequency, longer apnea duration, and worse oxygen desaturation during sleep.[16] In another study, flurazepam at high doses (30 mg) but not at lower doses (15 mg) increased SDB events in subjects with COPD.[17,18] Genta and colleagues[19] demonstrated the critical closing pressure (Pcrit) of the UA during midazolam-induced sleep is similar to the Pcrit during natural sleep.

Overall, the data suggest that low-dose benzodiazepines are relatively safe for patients with underlying lung disease or SDB and may improve periodic breathing associated with ascent to high altitude.

### *Nonbenzodiazepine Hypnotics*

Nonbenzodiazepine sedative hypnotics include zolpidem, eszopiclone, and zaleplon. They promote sleep by acting on a subset of the $GABA_A$ receptors. These agents have no significant adverse effects on respiratory patterns or $SaO_2$. The nonbenzodiazepine hypnotics have been investigated for treatment of high altitude periodic breathing, central apnea, and obstructive apnea. They have also been shown to enhance short-term adherence to continuous positive airway pressure (CPAP) therapy compliance.[20]

Eckert and colleagues[21] investigated the effect of eszopiclone on OSA. Seventeen subjects with OSA without significant nocturnal hypoxemia received eszopiclone (3 mg) or placebo. Eszopiclone increased arousal threshold and sleep duration, improved sleep quality, and lowered AHI without prolonging respiratory events or