Persistent Insomnia Despite Long-Term Nightly Use of Sleeping Pills

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A 57-year-old woman presented with difficulty in falling asleep and occasional perceived lack of sleep for the entire night despite taking sleeping pills every night for more than ten years. Prior to then, for no obvious causes, she gradually had difficulty falling asleep at night, daytime fatigue, sleepiness, and no energy. Afterwards, the insomnia symptoms gradually worsened. She then began to be very anxious about sleep and often sought medical assistance. After seeing her first physician, she began using 0.4-0.8 mg of alprazolam with inconsistent results—sometimes she felt better, sometimes not. Since the initial prescription of alprazolam, in attempts to get a better night's sleep, she frequently sought help from neurologists and psychiatrists, and was even hospitalized twice. This led to a variety of prescriptions including fluoxetine, paroxetine, sertraline, trazodone, mirtazapine, quetiapine, zolpidem, zopiclone, and eszopiclone. None of these medications significantly improved her sleep, and she felt that alprazolam was more helpful for her sleep than the other drugs. Therefore, she continued taking alprazolam and had gradually increased the dosage to 1.2 to 2.0 mg per night. She had also been diagnosed as having hypertension and had routinely taken antihypertensive medications for approximately six years. When we ran a symptom check for a sleep breathing disorder, we found that she had loud snoring and could truly fall asleep during the day, but did not know whether she had breathing pauses during sleep. No special findings were obtained in the routine medical examination and laboratory results. Her BMI was 23.42 kg/m², neck circumference was 36 cm, and she had a normal looking chin. Her total score on the Epworth Sleepiness Scale (ESS) was 22, which reflected her subjective severe excessive daytime sleepiness. Scores for the Hamilton depression and anxiety scales were 17 and 24, respectively, suggesting that she had had mild to moderate severity depression and anxiety.

Examination and Management at Sleep Laboratory

We arranged an overnight polysomnographic (PSG) examination followed by a multiple sleep latency test (MSLT). As shown in the top panel of

Figure 1, the patient had 7.4 h of total sleep, but had 367 obstructive apneas and 162 episodes and hypopnea, central, and mixed apnea/hypopnea. Her apnea/hypopnea index (AHI) was 72/h. There were marked recurrent reductions of oxygen saturation throughout the full night recording (see **Figure 1**). She had N2 time over 60% and no slow wave sleep (N3). However, when we asked her for her subjective sleep time after the examination, she said that she had no sleep during the entire night because she did not take alprazolam. The mean sleep latency on MSLT was only 2.3 min (**Figure 2**), and she also had one episode of REM during her third nap. This indicated that she had objective severe excessive daytime sleepiness.

A few days later, the patient was scheduled to receive auto nasal continuous positive airway pressure (CPAP) titration followed by MSLT. As shown in the center panel of **Figure 1**, she had 9.1 h of total sleep, and AHI was successfully reduced to 7/h. N1 and N2 time and number of awakenings and brief arousals were markedly reduced, whereas N3 and REM time were increased considerably. Associated with the improvement in overnight sleep, the mean sleep latency on MSLT the day following CPAP titration increased from 2.3 min to 9.9 min (**Figure 2**). When we asked her subjective feelings regarding overnight sleep and daytime functioning, she said that she had not had such wonderful sleep over the past ten years and that her energy during the day appeared be similar to that she had twenty years ago. She immediately began to receive CPAP therapy (ResMed, S8 Auto Set Spirit). Since that time, she has had much improved subjective overnight sleep and completely discontinued taking alprazolam after a week of CPAP treatment.

Nine months after she began to receive CPAP therapy, she was recalled for a follow-up evaluation. The memory card of the CPAP machine indicated that average usage was from 8 to 9 h per night, and that the average AHI was 6.1/h. As shown in the bottom panel of **Figure 1**, during CPAP pressure titration at this time, AHI was further reduced to 1.5/h; total sleep time, N3, and REM time were considerably reduced; and N2 time was increased more than twofold, compared to during the first CPAP pressure titration. The perception of sleep (calculated as

Figure 1—Changes of SpO₂ and histogram of sleep determined by PSG

Diagnostic night (top), first CPAP pressure titration following immediate diagnosis (center), second CPAP pressure titration nine months after diagnosis (bottom).

Figure 2—Multiple sleep latency test following CPAP pressure titration nights

First CPAP pressure titration following immediate diagnosis. Second CPAP pressure titration nine months after diagnosis.

[subjective TST / objective TST * 100] was 102%. The mean sleep latency on the MSLT was also prolonged to 14.6 min (**Figure 2**). The scores on ESS and Hamilton depression and anxiety scales were also back in normal ranges. She also unexpectedly reported that she had stop taking antihypertensive medications a few months after she began CPAP, due to her blood pressure normalizing.

QUESTION: What is your diagnosis?

ANSWER: Obstructive sleep apnea-induced chronic insomnia.**DISCUSSION**

There is little doubt that the patient had a severe obstructive sleep apnea (OSA)-induced sleep perception problem presenting as a subjective type of insomnia. The fact that she had little to no perceived sleep appeared to be related to poor quality of sleep (N1, 22%; N2, 61%; and no N3) induced by very frequent apnea events. The cause and effect relationship between severe sleep apnea and insomnia was clearly reflected in the considerable improvement in both subjective and objective overnight sleep after CPAP treatment. The nine month follow-up evaluation further indicated a cause and effect relationship.

OSA related insomnia was first reported in the early 1970s,¹ and recent studies suggest that possibly 25% to 50% of patients have both OSA and insomnia.² However, a high percentage of these patients have mild to moderate severity of apnea and do not fully comply with CPAP therapy; therefore, they do not receive much benefit with respect to perceived sleep.³ Due to the poor compliance with CPAP therapy, current opinion holds that it is very challenging to treat patients with OSA and insomnia. But, the successful diagnosis and treatment in this case illustrated that, at least for some patients, particularly for severe apnea related insomnia, CPAP therapy may produce a dramatic improvement in both subjective and objective overnight sleep, and in both subjective and objective daytime functioning.

The DSM-IV states that “most individuals with breathing-related sleep disorder have obstructive apnea that can be distinguished from primary insomnia by a history of loud snoring, breathing pauses during sleep and excessive daytime sleepiness.” This patient had at least two symptoms (snoring and daytime sleepiness); however, she mainly complained of severe insomnia and was never aware that her snoring might be associated with her insomnia. Thus, she never mentioned severe snoring to any physicians during her clinic visits. No family member witnessed her apnea. Most importantly, no physicians considered possible OSA and did not run any symptom check for OSA, even though she was hospitalized twice. This misdiagnosis led to her using 1.2-2.0 mg of alprazolam per night, which may have considerably aggravated her apnea and daytime sleepiness. In particular, since she had a history of hypertension, the misdiagnosis and the continual use of alprazolam could increase her life risk.

The fact that a variety of antidepressants were persistently prescribed over a long period, even with little improvement for her subjective sleep, suggests that neurologists and psychiatrists normally pay great attention to depression and anxiety in insomnia patients, but lack adequate awareness of OSA-related insomnia. This may be particularly true for countries such as China, where the training system for sleep disorder specialists has not been well established. Even in the United States, which has the most well-developed training system in sleep disorders, restrictions for reimbursement from medical health insurance companies, may make physicians reluctant to call for an overnight study to detect potential OSA-related insomnia.

On follow-up, we unexpectedly learned that her blood pressure was normalized after a few months of CPAP treatment, al-

though she had taken antihypertensive medications for six years. Though benzodiazepines may not worsen mild to moderate of OSA,⁴ their influence in severe OSA has not been experimentally documented. We believe that both the immediately successful treatment of her sleep breathing issue and the successful discontinuation of the relatively high dosage of alprazolam could have contributed to the normalization of her blood pressure.

CLINICAL PEARLS

1. Physicians may need to routinely run a brief symptom check in their insomnia patients to distinguish possible OSA patients, at least for the symptoms mentioned in the DSM-IV, including snoring, witnessed breathing pauses during sleep, and excessive daytime sleepiness.
2. Most individuals with OSA and insomnia comorbidities may not fully comply with CPAP therapy. But, at least for some severe apnea related insomnia, CPAP therapy may produce a dramatic improvement and may lead to discontinuation of sleeping pills.
3. In patients with hypertension and OSA-induced insomnia, reduction or normalization of blood pressure may occur after CPAP treatment, even in patients who have taken antihypertensive medications over a long period.

CITATION

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DISCLOSURE STATEMENT

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