Insomnia and Upper Airway Stimulation Therapy Benefit and Adherence: A Case Series

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Abstract

Obstructive sleep apnea (OSA) and insomnia are common sleep disorders that often occur concurrently. The presence of one of these disorders often negatively impacts the other, including affecting treatment benefit and adherence. While insomnia has been shown to adversely affect positive airway pressure therapy adherence, minimal data is currently available on the effects of insomnia on upper airway stimulation (UAS) therapy for the treatment of OSA. We present two cases that highlight the negative impact of insomnia on UAS therapy usage and OSA management as well as the benefits of insomnia treatment on overall outcomes. Screening for and treatment of insomnia prior to UAS implantation are recommended.

Keywords: cognitive behavioral therapy for insomnia (CBT-I), upper airway stimulation (UAS), obstructive sleep apnea (OSA), insomnia, co-morbid insomnia and sleep apnea (COMISA)

Insomnia and Upper Airway Stimulation Therapy Benefit and Adherence: a Case Series

Obstructive sleep apnea (OSA) is a result of repeated obstructions in the upper airway during sleep. Untreated OSA has been shown to be associated with a multitude of negative health effects as well as daytime symptoms. Positive airway pressure (PAP) therapy is the first-line treatment of moderate to severe OSA. Despite high efficacy with PAP in improving the apnea-hypopnea index (AHI) and OSA symptoms, adherence to PAP therapy limits its effectiveness as 46 to 83% of patients with OSA are nonadherent to PAP (Weaver et al., 2008).

For patients unable to tolerate PAP, upper airway stimulation (UAS) is a treatment option. The UAS system (Inspire Medical Systems, Inc, Maple Grove, Minnesota) is a Food and Drug Administration-approved treatment for moderate to severe OSA. Through a unilateral hypoglossal nerve implant, the UAS system works to maintain upper airway patency by tongue protrusion in response to the patient's respirations. UAS has been demonstrated to significantly reduce the AHI and to improve OSA-related symptoms, including sleepiness (Woodson et al., 2018).

OSA and insomnia are common sleep disorders. Co-morbid insomnia and sleep apnea (COMISA) is highly prevalent, affecting approximately 39 to 55% of adults (Sweetman et al., 2017; Luyster et al., 2010). Patients with COMISA have reduced quality of life and increased risk of daytime symptoms, depression, anxiety, hypertension, cardiovascular disease, and all-cause mortality compared to those without these conditions and either condition alone (Björnsdóttir et al., 2012; Smith et al., 2004; Sweetman et al., 2017; Lechat et al., 2021). Studies have shown that presence of insomnia can reduce PAP adherence, which is typically defined as at least 4 hours of PAP usage over a 24-hour period for at least 70% of days. However, treatment of insomnia may improve adherence to PAP therapy (Luyster et al., 2010; Wallace et al., 2018;

Wickwire et al., 2008; Pieh et al., 2013). Minimal data is currently available on the effect of insomnia and its treatment on UAS benefit and therapy adherence.

Individuals with insomnia may be hypersensitive to PAP therapy with compromised tolerance and adherence (Luyster et al., 2010). Similarly, these individuals may be more likely to experience hyperarousal associated with UAS therapy, as the subjective experience of UAS impulses can be described as uncomfortable by some individuals and may be particularly bothersome to those already having difficulty with sleep onset or maintenance. UAS is designed to begin after a delay period of up to 75 minutes, during which individuals should initiate sleep. However, individuals with insomnia may find the experience of UAS especially anxiety-provoking due to the inability to initiate sleep in the prescribed time. Additionally, increased awakenings and awareness throughout the night due to insomnia may interfere with maintaining consistent UAS use, as the patient will often need to pause or stop and restart the UAS device with nocturnal awakenings in order to return to sleep.

Consequently, UAS device use and benefit may be adversely impacted for those with insomnia. Cognitive behavioral therapy for insomnia (CBT-I), as the first-line treatment of insomnia, may be critical for individuals with concurrent UAS therapy for successful use and optimized results. The following cases of individuals with COMISA and UAS therapy demonstrate the effect of insomnia and its treatment on UAS adherence and outcomes.

Case 1

A 49-year-old woman with a past medical history including hyperlipidemia, depression, and restless legs syndrome was diagnosed with severe OSA by a home sleep apnea test (HSAT). The study demonstrated a respiratory event index (REI, or HSAT surrogate of the AHI) of 40.1/h

(normal <5/h) with an oxygen saturation nadir of 81% and 22.4 minutes with oxygen saturation levels <89%. PAP therapy was initiated; however, she was intolerant to PAP and subsequently underwent UAS implantation (Inspire IV Model 3028).

Per standard of care, two months after implantation the patient presented to the sleep medicine clinic for initial consultation and UAS system activation. At that visit, the patient reported sleep-onset and maintenance insomnia with an average sleep latency of over 1 hour and 5-6 recalled nocturnal awakenings per night with difficulties returning to sleep. She was spending about 10 hours in bed each night and napping twice a week.

During this initial sleep medicine clinic visit, UAS therapy was activated according to standard protocol. The patient was advised to raise the UAS amplitude (or amount of force the tongue moves forward with impulses) gradually by use of an external remote as tolerated during the time period between the activation and when she returned for the UAS titration sleep study approximately 3 months later. During the time leading up to the titration study, she was able to raise the amplitude 5 points on her remote but had to decrease once due to intolerance.

As planned, the patient returned to the sleep laboratory for the UAS titration study to evaluate control of sleep apnea on different UAS amplitudes. During the titration study, her sleep efficiency was 70.1% with 108.7 minutes of wake after sleep onset and an arousal index of 24.7/h. The overall AHI during the titration was 5.4/h, and at the optimal amplitude, the AHI was 0.0/h.

Despite good control of OSA with UAS, insomnia worsened and became a barrier to UAS use in the few weeks after the titration study. Figure 1A shows that at this point she was not using UAS at all on her data download. She reported lying awake waiting for the UAS impulses to start. The decision was made to temporarily cease UAS usage and focus on insomnia

management. She was referred to behavioral sleep medicine for CBT-I. With the behavioral sleep specialist, she reported a 25-year insomnia history following chronic family stressors, describing her sleep as “shallow” and “poor” even prior to her OSA diagnosis and UAS placement. She noted “disappointment” that the UAS placement did not improve her sleep, and insomnia symptoms were exacerbated by the patient’s discomfort with the UAS impulses as well as her attribution that her sleep was “hopeless” with little chance of improvement. She subsequently completed 4 sessions of CBT-I with marked improvements, achieving restorative sleep with reduced sleep-onset latency and unremarkable nighttime awakenings. Her CBT-I course followed standard protocol but was limited to 4 sessions due to a rapid positive response. Components of treatment included sleep hygiene, stimulus control, sleep restriction, relaxation training, cognitive restructuring to address negative beliefs and worries about sleep, and confidence building in her ability to create healthy sleep habits long term. A maintenance session was scheduled for 1 month following her last treatment session, but the patient cancelled this session due to good response.

The patient returned to the sleep medicine clinic after completion of the brief yet successful course of CBT-I. She reported an average sleep latency of 30 minutes and well-consolidated, refreshing sleep from approximately 11:00 pm to 7:00 am nightly. With insomnia much improved, she was ready to resume UAS therapy. Due to her history of intolerance, she was restarted on lower amplitudes. Her UAS usage improved (Figure 1B), and she was able to increase the UAS amplitude subsequently to optimally control her OSA.

Case 2

The patient is a 53-year-old man with a past medical history including insomnia, major depressive disorder, restless legs syndrome, post-traumatic stress disorder, and severe OSA. He was initially treated with PAP therapy; however, he was intolerant to this treatment despite many adjustments and ceased therapy. Several years later, he completed another sleep study conducted as an HSAT, which showed severe OSA with an REI of 38.8/h and an oxygen saturation nadir of 77% with 23.3 minutes spent with oxygen saturations <89%.

Due to his inability to tolerate and receive benefit with PAP, the patient pursued UAS therapy. The UAS system (Inspire IV Model 3028) was implanted and activated per standard protocol. Approximately 3 months after activation, he then completed an UAS titration sleep study where he was assessed on different amplitudes with an overall AHI of 58.3/h. OSA control only improved in non-supine, non-rapid eye movement sleep, and at the most optimal setting in the non-supine position, the residual AHI remained elevated at 16.0/h. He also had very frequent arousals from sleep during this study with an arousal index of 94.4/h, very little rapid-eye movement (REM, or stage R) sleep, and no slow-wave (or stage N3) sleep (Figure 2A). Further adjustments of the UAS settings were made, including changes in the amplitude to improve OSA control and also advanced setting changes for patient comfort. After the patient gradually increased the amplitudes over a few months, he completed an HSAT with UAS for 2 consecutive nights; however, these studies showed persistence of severe OSA.

The patient was seen in the sleep medicine clinic shortly after the HSAT, where he reported that his sleep was very poor at the time of the study due to worsening of his insomnia secondary to several life stressors. He also reported significant discomfort with UAS therapy in the setting of the insomnia. Additional UAS setting changes were made for comfort. However, UAS usage and tolerance continued to decline as insomnia worsened. Our multi-disciplinary

UAS team incudes sleep medicine, sleep surgery, and behavioral sleep medicine working closely to optimize patient outcomes, and it became clear that each discipline would be important to appropriately treat the patient. He was referred to behavioral sleep medicine for CBT-I to treat the insomnia and back to sleep surgery (otolaryngology) for an awake endoscopy due to the persistently elevated residual AHI. With awake endoscopy, advanced UAS settings can be tested during supine flexible pharyngolaryngoscopy and with several positional alterations. The procedure allows for determination of advanced UAS settings in an effort to optimize 1) visual upper airway opening to enhance AHI reductions and 2) patient comfort to enhance tolerance. Settings were changed again based on UAS response and comfort. Interestingly, these changes made following awake endoscopy resulted in the same setting changes made after the initial UAS titration study, where suboptimal control of sleep apnea was demonstrated by HSAT. Consideration of additional surgical intervention was discussed given the high residual AHI and suboptimal palatal recruitment during stimulation pulses on awake endoscopy.

Prior to additional surgery, however, an advanced UAS titration sleep study was recommended by the multi-disciplinary team, where settings other than amplitude can be changed during the study by a specialized sleep technologist to directly visualize which advanced settings most improve OSA. The patient called prior to the scheduled study indicating that his insomnia continued to worsen due to many increasing stressors. He reported sleeping an average of just a couple hours each night with significant sleep onset and maintenance difficulties, and he was uncertain that he would be able to sleep during the study. However, he was hopeful that the study would provide answers and improve his sleep, and he desired to proceed with testing if possible. The patient still had not initiated CBT-I as the patient traveled frequently for work and had been unable to coordinate appointments. As a result, the decision

was made to use eszopiclone 3 mg the night of the sleep study. Eszopiclone was chosen as he had been on this medication in the past and sleep maintenance was the predominant problem.

At the time of this second titration sleep study, he was using the UAS system < 1 h/day on average (Figure 3). Although prepared to make advanced UAS adjustments, no settings needed to be changed during the study other than amplitudes, which were assessed at lower settings than his initial titration study. His overall residual AHI was 0.7/h and oxygen nadir was 92%. Compared to the initial UAS titration study, the second study showed not only much improved overall residual AHI (0.7/h vs 58.3/h) but also markedly reduced arousal index (24.7/h vs 94.4/h), reduced end-tidal carbon dioxide levels, improved oxygen saturation, improved sleep efficiency, and improved sleep quality with increased percentages of slow-wave and REM sleep (Figure 2B). The patient reported tolerating UAS therapy well during the study and felt more rested and energetic the following morning.

Based on the marked improvements in OSA and sleep continuity as well as patient symptoms, the decision was made to continue eszopiclone 1 mg at bedtime as needed for insomnia until the patient could begin CBT-I. The patient was seen in the sleep medicine clinic a couple weeks after the second titration study and noted continued substantial improvements in sleep. He reported greater than 6 hours of sleep a night on average, much increased use and tolerability of UAS, and improvement in symptoms, including daytime functioning and sleepiness. The significant change in use before and after insomnia treatment with eszopiclone is visible on his UAS device download (Figure 3).

While waiting for CBT-I initiation, through the sleep medicine clinic the patient has started to work on components of CBT-I, including sleep hygiene, sleep restriction, stimulus control, and relaxation training. By taking these steps, he has been able to reduce his eszopiclone

use to <50% of nights. Further addressing the cognitive components is suspected to lead to further improvements and wean of eszopiclone.

Discussion

COMISA is extremely common and is associated with increased morbidity and mortality (Sweetman et al., 2017; Luyster et al., 2010; Björnsdóttir et al., 2012; Smith et al., 2004; Lechat et al., 2021). The cases presented here are the first reported in the literature that demonstrate the effects of insomnia on UAS therapy adherence and the potential benefits of insomnia treatment, such as CBT-I and/or pharmacotherapy. While reduced PAP adherence has been shown with insomnia, little is known about the effect of insomnia on UAS therapy. The only known published data at the time of this report is that from an abstract presented at SLEEP 2019, which showed 11 out of 20 veterans who underwent implantation of an UAS system had insomnia. The patients with insomnia were less adherent and showed less symptom improvement with UAS compared to those without insomnia (Wallace & Wohlgemuth, 2019).

Some patients may have improvements in insomnia by treatment of OSA alone and not experience barriers to OSA treatment. Guilleminault et al. (2008) showed that 1 in 3 patients treated for OSA had resolved insomnia. Another study showed that the timing of when insomnia symptoms occurred in the night was key in whether they resolved with OSA treatment alone. Sleep maintenance insomnia frequently improved with OSA treatment, but sleep-onset problems and early morning awakenings often persisted after 2 years of PAP therapy (Björnsdóttir et al., 2013).

For the two-thirds of patients with COMISA who do not experience a spontaneous resolution of insomnia with OSA treatment, insomnia treatment should be a necessary staged

intervention. Treatment of comorbid insomnia has been shown to improve PAP adherence in patients with OSA (Luyster et al., 2010; Wickwire et al., 2008). CBT-I is the recommended first-line treatment for insomnia (Schutte-Rodin et al., 2008). CBT-I is an effective, nonpharmacologic treatment for insomnia and may reduce the level of hyperarousal and stress associated with sleep. With CBT-I a multimodal approach involving cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation is undertaken. Significant improvements in sleep-onset latency, wake after sleep onset, total sleep time, and sleep efficiency are reported with CBT-I. These benefits are often maintained over time with continued improvements in post-treatment total sleep duration reported (Trauer et al., 2015). CBT-I may be superior to pharmacologic treatments both short-term and long-term in improving several sleep parameters, including slow-wave sleep duration, sleep efficiency, and wake after sleep onset (Sivertsen et al., 2006).

While CBT-I is the first-line treatment of insomnia, access to certified behavioral sleep medicine specialists is limited and the time commitment for CBT-I is difficult for some patients. In such cases, pharmacologic treatment may need to be considered for the treatment of insomnia. While our preference is to limit medication use, in the second case, the patient was not able to undergo CBT-I in a timely fashion and a brief trial of eszopiclone was initiated. In a double-blind, randomized crossover pilot study evaluating the effects of eszopiclone on sleep and respiratory parameters in patients with untreated OSA, eszopiclone did not worsen AHI, duration of respiratory event episodes, or oxygen saturation. Significant improvements in reduction of spontaneous arousals, sleep efficiency, and wake after sleep onset were seen with eszopiclone compared to placebo (Rosenberg et al., 2007). Another randomized, placebo-controlled trial showed that eszopiclone 3 mg in the first 2 weeks of PAP use in patients newly diagnosed with

OSA demonstrated improved PAP adherence and had decreased rates of discontinuation of PAP at 6 months compared to placebo (Lettieri et al., 2009). These studies suggest that eszopiclone does not worsen sleep-disordered breathing and can lead to improved sleep continuity and OSA treatment adherence. In this patient's case, insomnia treatment clearly correlated with significant improvement in UAS therapy use; however, the marked improvement in the residual AHI with insomnia treatment was unexpected. One possible explanation for the substantial improvement in the residual AHI is that in treating his insomnia the arousals from sleep reduced and sleep continuity improved, thereby improving respiratory stability. Consequently, by improving his sleep continuity, the UAS system may have been allowed to work as intended throughout the night rather than disrupted by frequent awakenings and respiratory variability. This case suggests that pharmacologic treatment may be a temporary acceptable alternative for patients with UAS therapy and insomnia when CBT-I is not available. However, the data from Sweetman et al. suggests that through reduced nocturnal arousals, we may see a similar benefit in respiratory stability and improved AHI with CBT-I as well (Sweetman et al., 2020).

The timing of comorbid insomnia treatment in relation to OSA treatment commencement may be of importance. A randomized controlled trial evaluated the effects of CBT-I on PAP therapy adherence in patients with OSA and comorbid insomnia. In the treatment group, 4 sessions of CBT-I were completed prior to PAP therapy initiation, whereas the control group had treatment as usual. The patients in the CBT-I group had approximately 1 hour more PAP usage per night, higher initial PAP acceptance, and lower rate of PAP therapy reduction over 6 months. As expected, insomnia measures also improved more in the CBT-I treatment group compared to the control group. Sleep parameters were significantly improved in the CBT-I group prior to commencement of PAP therapy, which the authors hypothesized played a determining role in the

higher rate of initial PAP therapy acceptance in this group. Initial acceptance was the main factor reported with increased usage at 6 months with the CBT-I group compared to the control group (Sweetman et al., 2019). Similarly, treatment of insomnia prior to initiation of UAS therapy may be important. The UAS device may exacerbate existing insomnia during the initial introduction phase due to hyperarousal and prevent adoption of long-term use for optimal OSA management. Additionally, the improvements in PAP tolerance with CBT-I brings attention to the importance of early screening for and treatment of insomnia in all patients undergoing evaluation and management of OSA. Early initiation of CBT-I may reduce the need for second line OSA treatments, such as UAS, and pharmacologic treatment of insomnia. A multidisciplinary sleep clinic involving behavioral sleep medicine would streamline optimal management of patients with COMISA.

To date minimal data is available on the presence of insomnia and its effects on UAS adherence (Wallace & Wohlgemuth, 2019) and whether treatment of insomnia improves use. Our clinical experience demonstrates a growing percentage of patients that have insomnia who have difficulties tolerating or adhering to UAS therapy, prolonging an already long process in these patients for optimal management of OSA. The cases presented above suggest that all patients under consideration of UAS therapy would benefit from screening for insomnia prior to implantation. Early management of insomnia with treatment such as CBT-I should be considered in all patients with OSA and prior to UAS device activation, especially if sleep onset difficulties or early morning awakenings are the predominant insomnia symptoms. Furthermore, the close relationship and communication between a multidisciplinary UAS therapy team can greatly enhance diagnosis, workup, and treatment of concurrent sleep disorders. Additional research on

the impact of insomnia and associated treatment on UAS therapy adherence and benefit is indicated, as well as the impact of a closely integrated UAS team on patient outcomes.

Abbreviations

AHI, apnea-hypopnea index (events/hour)

CBT-I, cognitive behavioral therapy for insomnia

COMISA, co-morbid insomnia and sleep apnea

h, hour

HSAT, home sleep apnea test

REI, respiratory event index (events/hour)

OSA, obstructive sleep apnea

PAP, positive airway pressure

UAS, upper airway stimulation

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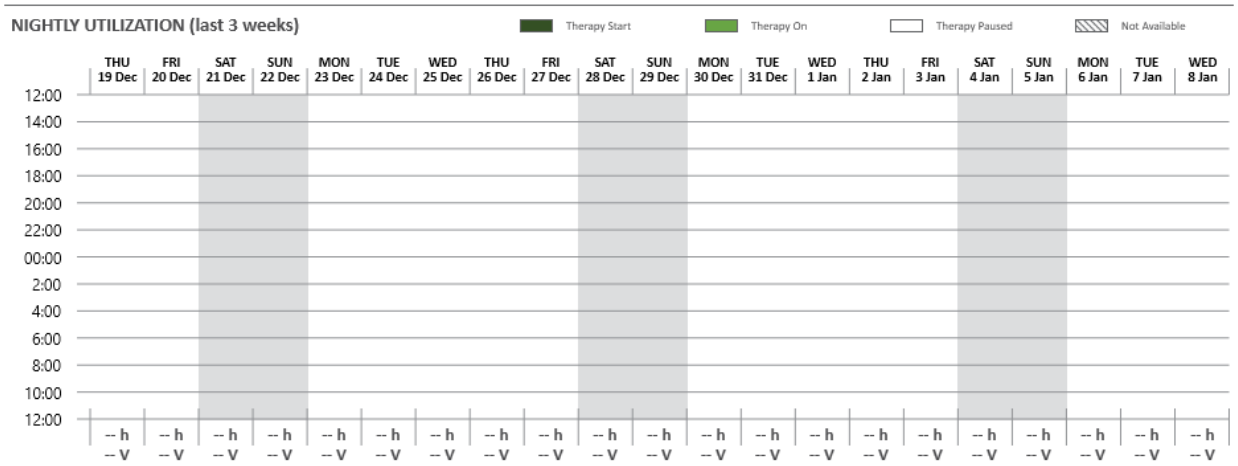
Figures

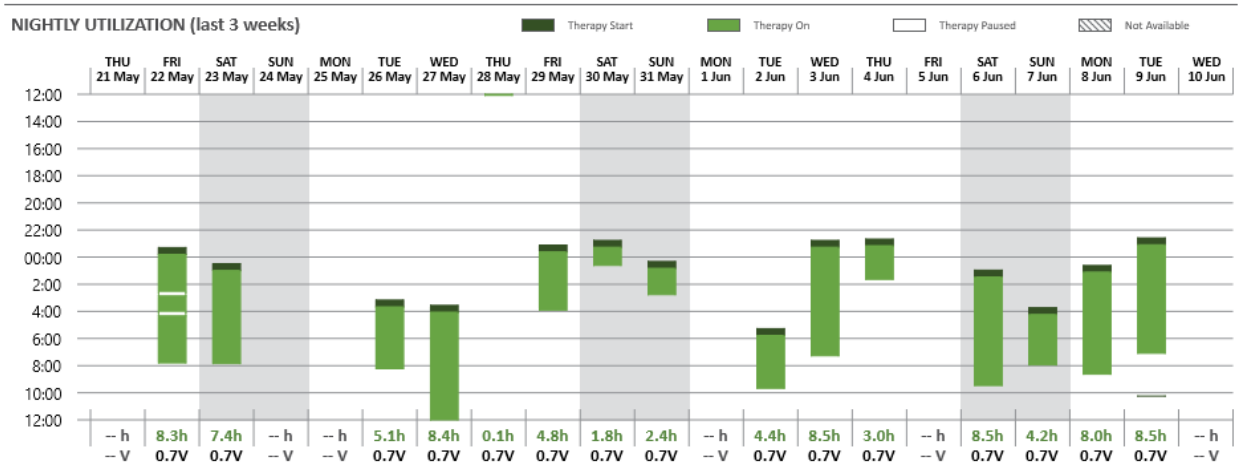
Figure 1

Case 1 - Upper airway stimulation (UAS) device download before (A) and after (B) cognitive behavioral therapy for insomnia (CBT-I).

A



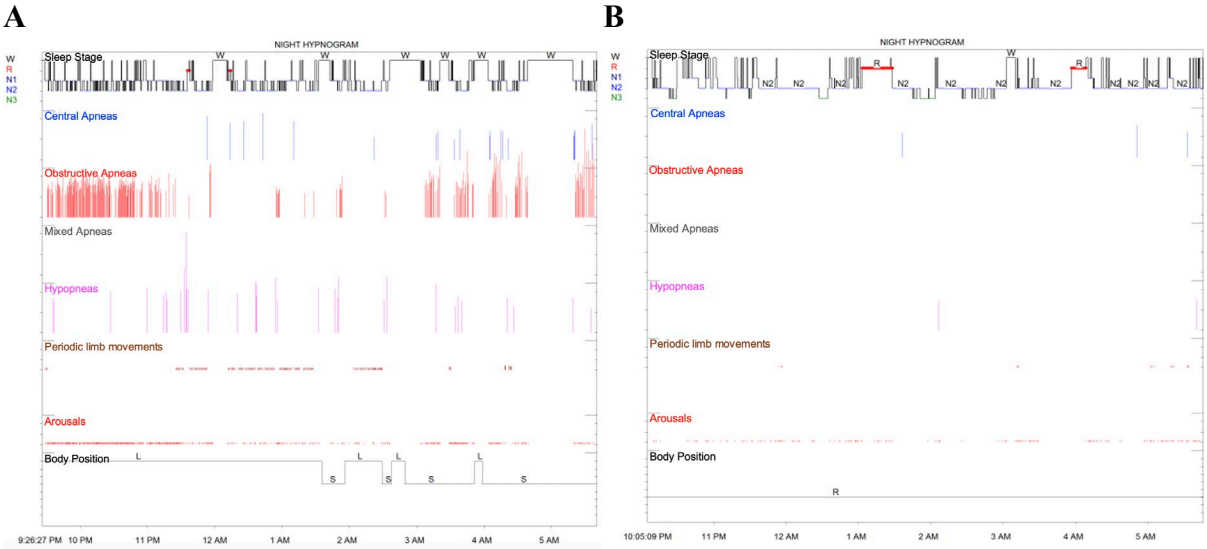
B



Note. After CBT-I, the patient was able to use UAS therapy most nights with infrequent pauses in therapy. h = hours, UAS = upper airway stimulation, V = volts (amplitude)

Figure 2

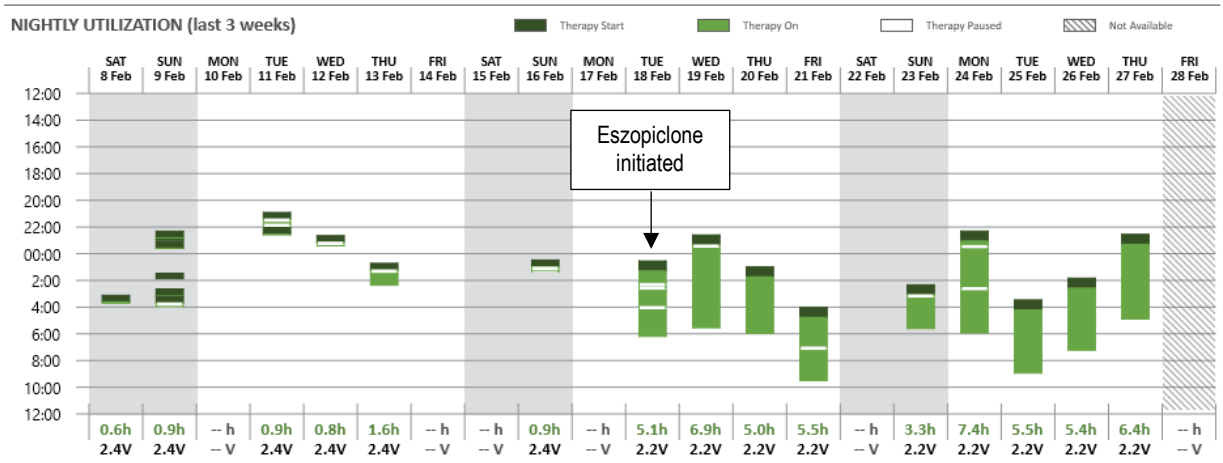
Case 2 - Hypnograms from the first upper airway stimulation (UAS) titration sleep study without insomnia treatment (A) compared to the second UAS titration study with insomnia treatment (B).



Note. Frequent respiratory events, frequent arousals, and poor sleep cycling were observed on the initial UAS titration study without insomnia treatment (A). Compared to the initial UAS titration study, on the second titration study (B) with eszopiclone for insomnia treatment markedly less respiratory events and arousals and improved sleep stage cycling. L = left lateral body position, N1 = stage N1 sleep, N2 = stage N2 sleep, N3 = stage N3 (slow-wave) sleep, R = REM sleep, R = right lateral body position, S = supine body position, UAS = upper airway stimulation, W = Wake.

Figure 3

Case 2 - Upper airway stimulation (UAS) device download before and after eszopiclone use.



Note. February 8th-17th is UAS therapy use without eszopiclone. The second UAS titration study occurred on February 18th where 3 mg of eszopiclone was used. February 19th-27th is UAS therapy use with eszopiclone 1 mg at bedtime. The patient did not use eszopiclone on February 22nd and was unable to fall asleep while using UAS therapy. He was seen in clinic on February 28th. h = hours, UAS = upper airway stimulation, V = volts (amplitude).