Austin Journal of Sleep Disorders

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Austin Publishing Group

Case Report

Opioid-induced Central Sleep Apnea Syndrome, a Case Study

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Received: January 12, 2015; **Accepted:** February 20, 2015; **Published:** February 24, 2015

Abstract

Although not as prevalent as obstructive causes of sleep disordered-breathing, central sleep apnea syndrome (CSAS) is a serious condition requiring close medical attention. The increasing rates of opium addiction as well as the frequent use of opioid analgesics have turned opioid-induced CSA to a more frequently encountered medical scenario in our sleep medicine practice. Here, we report a case with typical presentation of opium-induced CSAS, who referred to us with excessive daytime sleepiness characterized by irresistible need for daytime naps and cognitive lapses. The clinical characteristics, confirmation of diagnosis in polysomnography followed by the suggested care to such a patient are the focus of the present case study.

Keywords: Central sleep apnea; Hypopnea; Polysomnography; Opioid-induced; Excessive daytime sleepiness

Introduction

The majority of adult patients who undergo evaluation in sleep centers suffer from obstructive sleep apnea (OSA) and the diagnosis is usually confirmed based on the overnight polysomnography [1]. Although central sleep apnea (CSA) is not as prevalent as the obstructive type, we tend to see increasing number of such patients of which some report opioid abuse or extensive use of opioid analgesics. Excessive daytime sleepiness (EDS) is often the chief complaint of these patients when referred to the sleep clinic [2]. Clinicians need to be well-versed about the clinical significance of central sleep apnea syndrome as well as its opioid-induced type upon evaluating or referring suspected cases. When the diagnosis is confirmed, entering drug cessation programs, pharmacotherapy as indicated, close medical follow up, and possibly the use of continuous positive airway pressure (CPAP) are amongst the therapies controversially advocated in the literature [2,3].

Case Presentation

Presenting illness

N.A, a 55year-old male was evaluated with the chief complaint of excessive daytime sleepiness (EDS) and frequent pauses in breath during sleep over the past 5 years. The patient's problem along with continued sleep snoring were aggravated over the last 6 months prior to presentation to our sleep clinic. Although the patient reported EDS, his Epworth Sleepiness scales score marginally higher than normal (10/24). He further complained of unrefreshed morning wake ups with problem in maintaining nocturnal sleep since long.

The patient had been going to bed between 11pm and 12 am and waking up between 7 am to 8 am. With a self-reported short sleep latency of almost 5 min, and the average total sleep time (TST) of 7-8 hours, he complained of frequent nocturnal awakening with unknown trigger. He however had no problem returning back to sleep easily. The patient had unintentional, irresistible 2 to 3 naps each for nearly 1.5 hours during the day, feeling temporarily refreshment upon awakening. The patient reported no typical symptom for narcolepsy, restless legs syndrome or post-traumatic stress disorder (PTSD) but revealed symptoms compatible with parasomnia such as sleep walking, sleep talking and nightmares disorder.

Clinical history

He reported 3 motor vehicle accidents and several near accidents secondary to his excessive somnolence over the past 2 years. The patient's past medical history was positive for coronary artery disease (CAD) stable on medical therapy, hyperlipidemia, hypertension and cardiac arrhythmias (over the past 2 years), whereas unremarkable for thyroid disease, chronic obstructive pulmonary disease (COPD), asthma, allergy, and diabetes. Six months prior to presentation, the patient experienced a cerebral transient ischemic attack (TIA) with instant recovery and no significant sequelae.

He has been a 30 pack/year cigarette smoker with decreased smoking since the TIA occurred. The patient has been inhaling opium for more than 5 years while decided to cease opium inhalation since 5 months prior to presentation. He therefore entered the methadone maintenance therapy (MMT) under a psychiatrist's care receiving 30-50 mg methadone PO/d for two months after which he switched to use opium tincture instead of methadone. He has been using high doses of opium tincture (5-6 mL/day), often beyond the prescribed regimen, over the last three months prior to his current presentation to our sleep center. The history was negative for alcohol or other substance abuse. His medication history included Clopidogrel 75

Citation: Torabi-Nami M, Mehrabi S, Borhani-Haghighi A and Derman S. Opioid-induced Central Sleep Apnea Syndrome, a Case Study. Austin J Sleep Disord. 2015;2(1): 1008.

Table 1: Analysis of sleep stages. TIB: time in bed, REM: rapid-eye movement.

Sleep stages			
TIB (h)	7:20:49		
Total sleep time (h)	6:19:00		
Sleep efficiency (%)	86.0%		
Sustained Sleep eff. (%)	88.2%		
Sleep latency	0:11:19		
REM latency	0:33:00	41847.96	
Sleep stage change index	37.02	272	
	Duration	(%) TIB	(%) Sleep time
Wake	0:53:49	12.2%	0.0%
REM	1:03:00	14.3%	16.6%
Stage 1	0:32:00	7.3%	8.4%
Stage 2	2:37:30	35.7%	41.6%
Stage 3	2:06:30	28.7%	33.4%

mg PO QD, Atorvastatin 4o mg PO QD, Aspirin 80 mg PO QD, Nitrocantin 6.4 mg PO QD, Sodium Valproate 200 mg BID and Opium tincture 5-6 mL/d.

The family history was insignificant for OSA or other sleep disorders. On physical examination, he was found to have a BMI of 33.5, neck circumference of 39cm and an oropharyngeal Mallampati score of 2. The patient had a decreased motor power and hyperreflexia in his left lower extremity. No other remark in general and neurological examination was noted.

Evaluations and results

Given the severity of his symptoms (i.e. EDS and sleep disordered-breathing complaints), he underwent polysomnography (PSG) (using the SOMNO screen System and the DOMINO analysis software) at our sleep disorders laboratory. His overnight PSG study revealed a total sleep time (TST) of 06h: 19min and the total time in bed (TIB) of 07h: 20min (sleep efficiency of 86%). Study showed a non-rapid-eye movement (NREM) sleep latency of less than 20 min and rapid-eye-movement (REM) latency of 33 min. Sleep stages analysis are summarized in Table 1. The patient was found to be continuously snoring with the snore index and snore fraction of 558.68 and 71.7%, respectively. He had 539 apnea events with an apnea-hypopnea index (AHI) of 77. Most flow limitations (41 events with the index 6.3) occurred during NREM sleep (Table 2). Central sleep apnea events were found quite frequent throughout the study except in stage W (wakefulness). There were frequent O_2 desaturation episodes (n=159) with the desaturation index of 25.49, the baseline SpO_2 of 82% and the nadir SpO_2 of 57% during some central and mixed apnea events mainly in NREM sleep. Desaturation- and respiratory-related microarousals constituted 53% and 20% of all arousals during the study, respectively. There were no significant findings to suggest periodic leg-movement during sleep (PLMS).

Having this PSG study scored based on the latest AASM (American Academy of Sleep Medicine) manual for the scoring of sleep and associated events [4] and reviewing the analysis, the diagnosis of opium-induced central sleep apnea syndrome was made. The selected 300-second epochs demonstrating central and mixed apnea or hypopnea events are demonstrated in Figures 1, 2 and 3. Such respiratory events and the resultant frequent O_2 desaturation were mainly attributed to opium-induced central sleep apnea syndrome (CSAS). The patient was advised to discontinue or at least cut the opium tincture dose by half and refer to sleep laboratory in 3 months for continues positive airway pressure (CPAP) titration and therapy. Meanwhile, he was prescribed medroxyprogesterone acetate 30 mg

Table 2: Analysis of the respiratory events and snoring during the patient's PSG study. A: apnea, H: hypopnea, AHI: apnea-hypopnea index, NREM: non-rapid-eye movement, REM: rapid-eye movement.

Respiratory analysis						
	Obstructive	Mixed	Central	Total A.	Total H.	A+H
Number	40	95	404	539	1	540
Index	5.7	13.5	57.6	76.8	0.1	77
	REM	NREM	Sleep			
Apnea	26	513	539			
Apnea index (/h)	52.9	78.6	76.8			
Hypopnea	-	1	1			
Hypopnea index (/h)	-	0.2	0.1			
Flow Limitation	3	41	44			
Flow Limitation index (/h)	6.1	6.3	6.3			
Max. apnea duration (s)	87	74	74			
Max. hypopnea duration (s)	-	9	9			
Average apnea dur. (s)	30.1	22.4	22.7			
Average hypopnea dur. (s)	-	9	9			
AHI (/h)	52.9	78.8	77			
Snore analysis						
	All	Prone	Supine	Left	Right	Upright
Snore (Number)	3529	95	372	3062	0	0
Snore-Index	558.68	537.74	654.87	549.57	0.00	0.00
Snore absolute (min)	63.8	2.0	8.8	53.0	0.0	0.0
Snore episodes (min)	271.6	9.8	24.9	236.9	0.0	0.0
Snore fraction	71.7%					

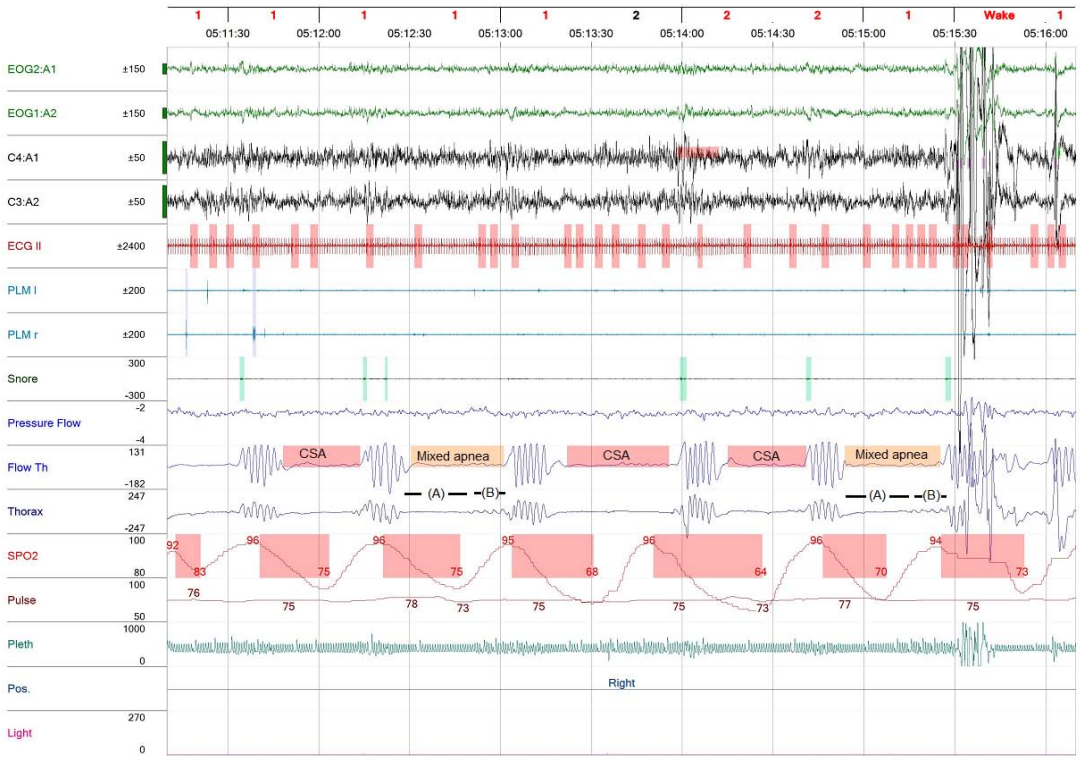

Figure 1: A 300-second snapshot from the patient's PSG study demonstrating central and mixed sleep apnea events in N1 and N2 sleep stages. Mixed apneas comprise an initial central event (A) followed by obstructive sleep apnea (B). CSA: central sleep apnea.

PO BID and acetazolamide 250 mg PO 1h before nocturnal sleep with biweekly follow ups for clinical assessment. ENT, cardiology and psychiatry consultations were sought to ensure proper evaluations for upper airway patency before CPAP therapy, cardiac assessments and optimized opium maintenance dose protocol, respectively.

Discussion

Substance abuse and the opium addiction in particular have increasingly turned into a societal and heath burden especially in developing countries. Moreover, since 15 years ago and following the release of the American Academy of Pain Medicine- and the American Pain Society's joint statement [5], opioid analgesics are often being aggressively used for pain control not only in pain clinics but also general practice.

This typical presentation with CSAS in an opioid-abusing subject prompted us to review and discuss this case.

Opioid receptors are nested in different parts of the brain while predominantly found in the brainstem either inside or in the vicinity of respiratory centers such as the medullary pattern generators and the nucleus of the tractus solitarius. The three types of opioid receptors include mu, delta and kappa. When most of the opioid substances target the mu type receptors, these receptors have the most inhibitory effect on the rate and amplitude of one's respiration [6].

While the role of opioids on respiratory function during wakefulness has long been acknowledged [6], our understanding on their role in breathing during sleep is relatively recent.

In a study where 50 patients on MMT (methadone is a mu opioid receptor agonist) were compared to 20 age- and sex-matched control subjects, findings showed 30% of the MMT subjects vs. no controls to have central sleep apnea (CSA) [7]. CSA was defined as an AHI of 5 or more where in more than 20% of MMT subjects, AHI was reported above 10. The rate of OSA was not different between MMT and control groups [7]. It has been hypothesized that the increased risk of CSA in MMT is linked to the imbalance between the central and peripheral chemoreceptors. In CSA, where the central chemoreceptors are inhibited, the peripheral receptors are enhanced and the stimulation of breathing following mild hypoxia would intermittently drive CO_2 below the apnea threshold [6,7].

There are other reports which provide evidence on the prevalence of opioid-induced CSAS in populations other than MMT subjects [8]. The common sleep disordered-breathing (SDB) is found in chronic opioid users includes CSA, ataxic breathing and sustained hypoxemia. Loud snoring and witnessed pauses during sleep are the most common symptoms reported by the patients or their family. As a result, fatigue and EDS may become significant symptoms following poor-quality sleep and frequent apnea and hypopnea events experienced in these individuals.

A historical cohort comprising 60 chronic opioid users and 60 sex- and age-matched control subjects [9], similarly reported a higher AHI in the opioid group as compared to controls. The breathing events were almost entirely central apneas. The opioid-using subjects' AHIs were correlated with the dose of opioids and inversely correlated with their BMI [9]. In a larger study, among 147 patients who underwent

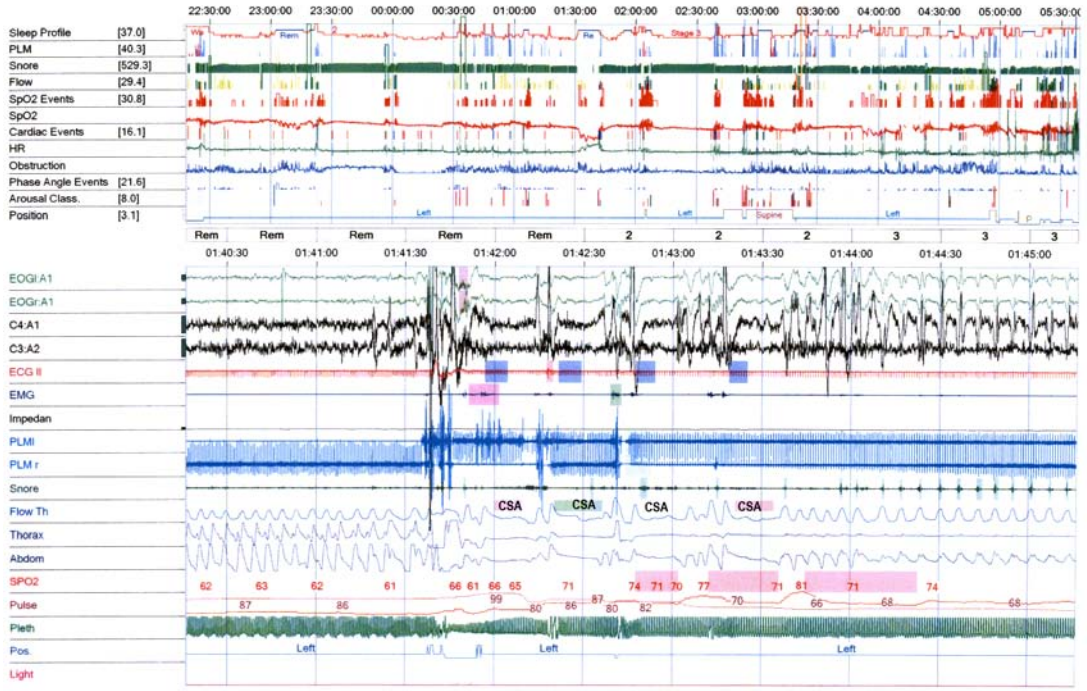

Figure 2: A 300-second epoch from the patient's PSG study representing samples of central sleep apnea events during REM and N2 sleep resulting in significant desaturations. C4A1 and C3A2 are the right and left central electroencephalographic tracings, respectively. CSA: central sleep apnea.

opioid pain control due to cancer, results from PSG confirmed the diagnosis of CSA, CSA with OSA, and OSA alone in 24%, 8% and 37% of the subjects, respectively. In line with other investigations, this report also demonstrated a dose–response relationship with CSA [10]. Therefore, with respect to the sleep-breathing parameters, these opioid analgesic users were found to be somehow similar to the MMT patients [9,10].

While CSA is not common in general population, some episodes of CSA which occur upon sleep onset in some individuals, may cause a transient alteration in consciousness level leading to brief arousals and related hyperventilation secondary to CO_2 chemosensitivity [6]. In the process of dozing off, arousals and falling back to sleep, the rise in CO_2level and the fall in O_2 lead to arousals driving CO_2 levels below the apnea threshold. This process goes on until the subject enters deeper sleep where fewer arousals tend to occur [3,6].

Cheyne–Stokes respiration (CSR) is another CSA type which has recently received more attention. The initiation and persistence of this condition largely depend on the apnea threshold while the condition differs from other CSA types with its typical crescendo–decrescendo breathing pattern following CSA. Cheyne–Stokes respiration is often associated with congestive heart failure and, when present, there is a higher mortality rate as compared with the matched heart failure controls with similar ejection fractions [11]. Cheyne–Stokes respiration is found to be a prevalent presentation in congestive heart failure and supratentorial stroke [11]. Other causes of CSA may include multiple sclerosis [12], cerebral infections [13], and hypoxemia of higher altitudes [14].

In the course of clinical presentation of our discussed case, several features were in favor of opium-induced CSAHS, whereas some features such as high BMI (33.5 kg/m2) did not comply with CSA. A vast majority of OSA patients are overweight or obese and obesity is perhaps the most important risk-factor for OSA, however, this is reported not to be the case with opioid-induced CSA (or other types of CSA). In fact, the AHI in CSA is shown to be inversely proportional to BMI [7]. One possible explanation for this reverse association might be the enhanced peripheral chemosensitivity in thin individuals [6].

Opioid users generally have a distorted sleep architecture [7]. Unlike OSA in which apneas predominantly take place during REM, in opioid-related CSA, respiratory events mainly occur during NREM sleep [1]. In the opium-induced CSAS patient described here, much of the flow limitation and hypopnea as occurred during NREM. The respiratory drive in NREM and particularly N3 stage of sleep (where delta waves are dominant) largely depend on the metabolic variables such as pH and blood gases, while breathing during REM is predominantly governed by signals from the medullary respiratory centers as well as higher cortical regions. Furthermore, respiratory responses toCO_2 and O_2 are depressed during REM sleep [15]. Other factors such as hypotonicity of the upper airway, may further explain why obstructive apneas tend to be dominant in REM sleep.

There are no sufficient data on CSA outcome following discontinuation of the culprit medication [2]. The presented case was advised to possibly discontinue or cut the dose of opium tincture to half to enable further therapeutic steps including CPAP therapy. In addition to discontinuation or optimization of opium dose, we expect CPAP to serve as an effective component in improving this patient's breathing during sleep although randomized data to support the same is inconclusive [2].

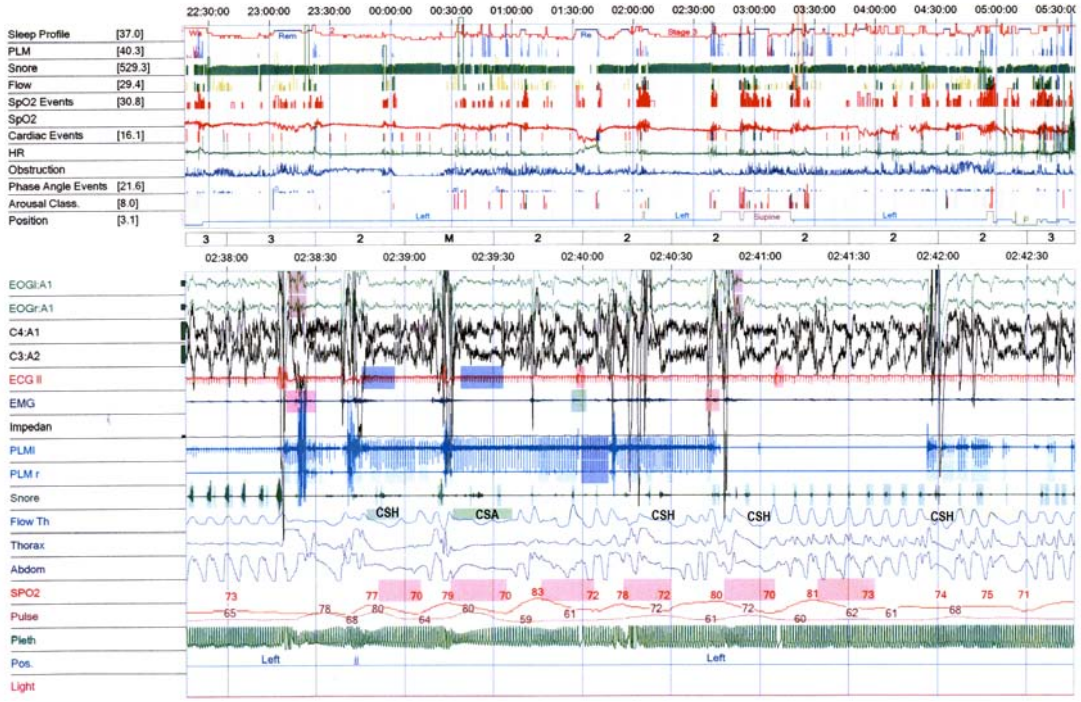

Figure 3: A 300-second epoch from the patient's PSG study showing samples of central apnea and hypopnea as in stage N2 sleep associated with significant desaturations. C4A1 and C3A2 are the right and left central electroencephalographic tracings, respectively.CSA: central sleep apnea, CSH: central sleep hypopnea.

There is no well-defined clinical pathway for the management of CSA of various etiologies. Meanwhile, a number of therapies have been field-tested with variable outcomes. Only several years following the approval of CPAP in OSA, it was advocated to be used in CSA [2]. CPAP may prevent over breathing and consequently prevent the reduction of CO_2 below the apnea threshold. When available, bi-level positive airway pressure (BiPAP) and adaptive servo ventilation (ASV) with and without oxygen supplementation can be sought as a potential alternatives. In a meta-analysis, BiPAP was shown to achieve elimination of central apneas in more than 60% of patients [2]. However, the other alternative, ASV, yielded conflicting results with almost 60% of participants attaining a central apnea index <10 per hour [2]. In general, the presence of ataxic breathing and Cheyne-Stokes respiration predict the poor response to PAP therapy [2,16-19]. With the increasing use of opioids, more investigations are required to define optimal PAP therapy and predictors of response in such a group of patients.

Studies on pharmacological therapy for CSA have yielded more controversial results. There are several drugs including theophylline (inhibiting adenosine receptors) [20], acetazolamide (inducing metabolic acidosis) [21], serotonergic medications (clomipramine, a serotonin reuptake inhibitor) [22] and medroxyprogesterone (stimulating respiratory centers) [23,24] which have been suggested to help CSA. Except for acetazolamide and, to some extent medroxyprogesterone, there seem to be no encouraging data to widely advocate pharmacotherapy in CSA. On the other hand, O_2 supplementation in CSA has gained positive evidence. O_2 may eliminate the hyperventilatory response to hypoxia and prevent CO_2 to drop below the apnea threshold. Although CO_2 administration would possibly act in a similar way, its use in clinical setting does not seem to be as feasible as O_2 [2,3].

Conclusion

Although non-obstructive causes of sleep-related breathing disorders are less frequent than OSA, the extensive use of opioid analgesics and opioid abuse has raised a red flag for opioid-induced CSA in our practice. The prevalence of substance-related sleep disorders and particularly opium-induced CSAS appears to be on the rise. Even in MMT programs, the prescribed "presumably safe" dose is often exceeded and sleep-breathing is seriously affected. When such cases with EDS and poor functionality due to sleep complaints are encountered, a thorough history taking and clinical evaluation suggest the diagnosis. Polysomnography is usually performed to confirm the diagnosis and to ensure proper PAP titration.

Acknowledgment

Authors would like to thank Ms. E. Cheraghipour for her assistance in preparation of this report.

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Austin J Sleep Disord - Volume 2 Issue 1 - 2015
ISSN : 2471-0415 | www.austinpublishinggroup.com

Citation: Torabi-Nami M, Mehrabi S, Borhani-Haghighi A and Derman S. Opioid-induced Central Sleep Apnea Syndrome, a Case Study. Austin J Sleep Disord. 2015;2(1): 1008.