Sleep Disordered Breathing Caused by Chronic Opioid Use

Diverse Manifestations and Their Management

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KEYWORDS

• Central sleep apnea • Obstructive sleep apnea • Ataxic breathing • Biot breathing
• Hypoglossal nerve • Pre-Bötzinger complex • Positive airway pressure • Ampakines

KEY POINTS

- Obstructive and central apnea and hypopneas, accompanied by cluster and Biot breathing, are common in patients on chronic prescription opioids for noncancer pain. Moreover, sustained hypoxia is noted between respiratory events on polysomnography and hypercapnia is present in a small percentage of patients.
- Opioid-related sleep disordered breathing (SDB) is probably mediated via binding to the pre-Bötzinger complex, hypoglossal nerve nucleus, and chemoreceptor sites.
- Increased hypoxic ventilatory responsiveness, and reduced hypercapnic responsiveness with hypoventilation, may be factors responsible for ventilatory instability during non–rapid eye movement sleep in chronic methadone users.
- Positive airway pressure (PAP)–based therapies offer variable success in eliminating SDB, with adaptive pressure support likely being the most effective. However, long-term outcome data with PAP therapies are not available.
- Ampakine-based therapies are novel agents that counter opioid-induced ventilatory depression without altering their analgesic effect.

INTRODUCTION

There is an epidemic of prescription opioid use in the United States. Since 1999, sales of prescription opioids have quadrupled.[1] Approximately 11.2% of the adult US population experiences chronic pain[2] and chronic noncancer pain is one of the main reasons for the increase in opioid analgesic use in the United States at a cost of $560 billion to $635 billion annually in medical costs and lost productivity.[3,4] The use of opioid analgesics for pain increased from 3.2% of the population from the period 1988 to 1994 to 5.7% during the period 2005 to 2008.[3] Non–schedule II opioids were the most common

Conflicts of Interest: None.

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Sleep Med Clin ■ (2017) ■–■
http://dx.doi.org/10.1016/j.jsmc.2017.07.007
1556-407X/17/Published by Elsevier Inc.

type of opioid used in long-term opioid therapy.[5] Notably, prescription pain relievers and heroin were also the main drugs associated with overdose deaths. In 2012, 259 million opioid prescriptions were written.[6] The rate of opioid overdoses tripled in the United States since 2000 to 28,647 deaths and accounted for 61% of all drug overdose deaths.[7] To counter the increasing number of opioid deaths, the Centers for Disease Control and Prevention (CDC) published practice guidelines in 2016 for safe prescribing of opioid medications for chronic pain conditions.[1]

Hypoventilation with terminal apnea is presumed to be a major of cause of death because many of these deaths reportedly occur during sleep, with no cause found at autopsy, except blood opioid levels. This article portrays the clinical features of opioid-induced sleep disordered breathing (SDB), investigates the potential pathophysiologic mechanisms for opioid-induced sleep apnea and provides the recent therapeutic advances for the treatment of chronic prescription opioid–induced SDB.

CLINICAL MANIFESTATIONS

Opioid-induced Sleep Disordered Breathing

SDB associated with opioids is distinct (**Fig. 1**) and has been extensively reviewed previously.[8–10] Briefly, these types of SDB include hypoventilation and, most commonly, mixed central and obstructive apneas and hypopneas. These events occur amid chaotic breathing patterns hitherto referred as ataxic breathing. This pattern is easily distinguished from the Hunter-Cheyne-Stokes breathing observed in patients with heart failure. In the background of ataxic breathing pattern, a cluster pattern and Biot breathing can be distinguished. Cluster breathing is characterized by cycles of deep breaths in which the amplitude of tidal volume is fairly stable with interspersed central apneas of variable durations. The Biot pattern is characterized by variable breathing rate and amplitude of tidal volume (discussed later).

Central sleep apnea

It is well established that opioids cause ventilatory depression. Moreover, recent studies have established that patients receiving chronic opioid therapy for chronic pain have an increased

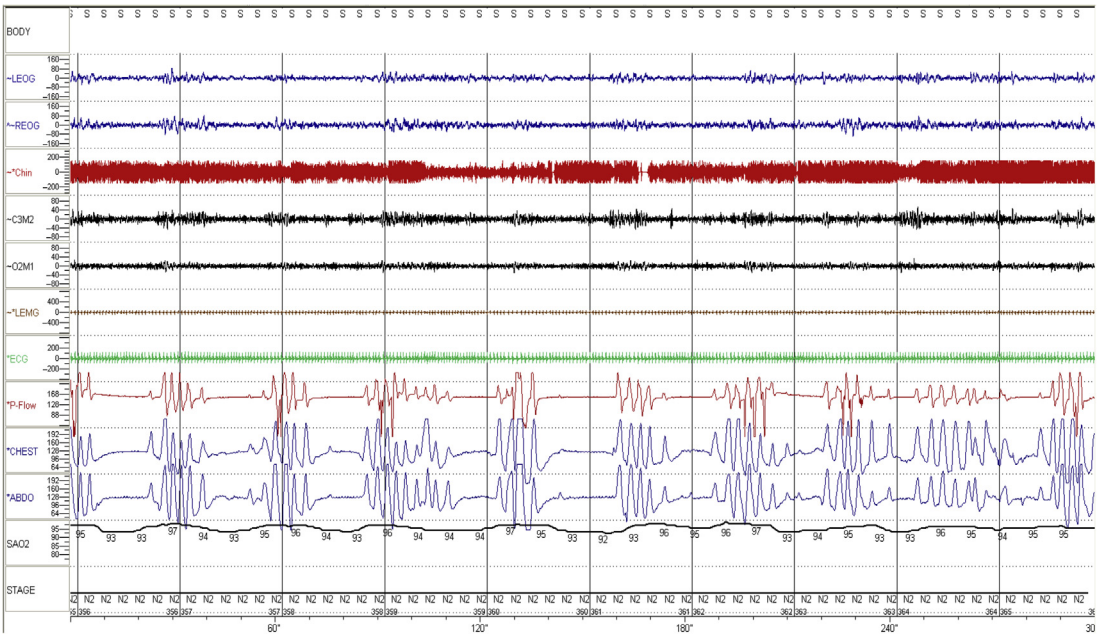

Fig. 1. A 5 minute-epoch of a polysomnogram showing obstructive (OSA) and central (CSA) apneas, and hypopneas in stage N2. There are repetitive central apneas with typical ataxic breathing pattern associated with opioids showing a mixture of Cluster and Biot's patterns. With CSA the airflow channels are flat associated with absence of effort on the thoraco-abdominal excursions. Also note fluctuations in SaO_2, which parallel the central apneas. Montage channels in descending order: body position, left electrooculogram (LEOG), right electrooculogram (REOG), chin electromyogram (EMG), central EEG, occipital EEG, leg EMG, pressure transducer, rib cage respiratory inductance plethysmography, abdomen respiratory inductance plethysmography, SaO_2, sleep stage.