Opioid Medication and Sleep-disordered Breathing

Herbert J. Yue, MD, Christian Guilleminault, MD, DBiol*

KEYWORDS

• Opioids • Sleep-disordered breathing
• Control of breathing • Sleep apnea

In recent years, there has been a growing recognition of chronic pain that may be experienced by patients. Historically, chronic pain has been given less importance or simply ignored by many practitioners, with deleterious effects on patients. There has been a movement toward treating these patients aggressively with pharmacologic and nonpharmacologic modalities. Opioids have been a significant component of the treatment of acute pain, with increasing use in cases of chronic pain, albeit with some controversy.[1,2] In addition to analgesia, opioids have many accompanying adverse effects, particularly with regard to stability of breathing during sleep. This article reviews the existing literature on the effects of opioids on sleep, particularly sleep-disordered breathing (SDB).

EPIDEMIOLOGY OF NARCOTIC USE

Despite the widespread use of opioids in varying aspects of medical practice, there are limited data on the specific usage or prescribing patterns of the most popular opiate medications. The Automation of Reports and Consolidated Orders System (ARCOS) is a mechanism whereby the Drug Enforcement Agency reports the amounts of opiate medications distributed on a retail basis. The data provided by ARCOS reports are limited in the sense that (1) veterinary usage is included, (2) usage of opioids for nonanalgesia indications are not specified, and (3) they do not include medications that were ultimately reordered or not distributed to patients.[3] The data subsequently represent an overestimate of the quantities of opioids used for human consumption.[3] Nevertheless, the amounts likely prescribed to patients remain substantial. In 1990, more than 2.2 million g of morphine was used medically, including 3273 g of fentanyl, 1.6 million g of oxycodone, and 118,455 g of hydromorphone.[4] When follow-up data in 1996 were evaluated, the use of fentanyl had increased by

Division of Sleep Medicine, Stanford University School of Medicine, Stanford Medical Outpatient Center, 450 Broadway Street, Pavillon C, Redwood City, CA 94063-5074, USA
* Corresponding author.
E-mail address: cguil@leland.stanford.edu

Med Clin N Am 94 (2010) 435–446
doi:10.1016/j.mcna.2010.02.007 **medical.theclinics.com**

1168%, followed by morphine with an increase of 59%, oxycodone by 23%, and hydromorphone by 19%. The only opioid medication to drop in usage was meperidine (5.2 to 3.2 million g). This significant increase in the prescribing of opioids is important, because they are known to have deleterious effects on the control of respiration, particularly during sleep.

CONTROL OF NORMAL BREATHING WHILE AWAKE AND DURING SLEEP

Control of normal breathing is a complex interaction between central respiratory pacemakers and interactions with central and peripheral chemoreceptors and mechanoreceptors. This control is also subject to alterations by voluntary and involuntary behavioral controls. To understand the effects of opioids on SDB, it would be useful to discuss the normal control of breathing in awake and sleep states.

Central respiratory rhythm generators, as well as those responsible for other behaviors such as swallowing and suckling, are located in the pontomedullary reticular formation.[5] In neonatal animals at least, a collection of neurons called the pre-Bötzinger complex has been shown to have properties consistent with a central respiratory pacemaker. A similar structure has not yet been found in humans. The pre-Bötzinger complex is found within the rostral ventrolateral medulla oblongata and contains neurons that produce rhythmic bursts of respiratory-like activity.[5] Even when the downstream activity of these neurons is interrupted pharmacologically, the neurons continue to fire in a rhythmic pattern, supporting their potential role as central respiratory pacemakers.[5] Interruption of the pre-Bötzinger complex is associated with irregular breathing patterns, particularly during sleep.[6,7] Another area important in central respiratory pattern generation is the retrotrapezoid/parafacial respiratory nucleus, also located in the ventrolateral medulla oblongata. Neurons with pacemaker activity have also been found in this area, and it seems that both these structures (the pre-Bötzinger complex and retrotrapezoid/parafacial respiratory nucleus) are required for normal respiratory rhythm.[8,9]

Interactions between respiratory pattern generators and central and peripheral receptors are a large determinant of the control of breathing. Metabolic control of breathing involves reflex and tonic inputs from peripheral and central chemoreceptors that detect changes in carbon dioxide (CO_2)/oxygen (O_2) levels or pH. The central chemoreceptors are located in several locations, particularly the nucleus tractus solitarius, dorsal respiratory group, medullary raphe, pre-Bötzinger complex, and the retrotrapezoid/parafacial respiratory group.[5,10] These chemoreceptors are sensitive to changes in the partial pressures of carbon dioxide/pH, and increase both tidal volume and/or respiratory rate in response to hypercapnia or acidemia. Peripheral chemoreceptors consist of collections of neurons that detect changes primarily in the partial pressure of arterial oxygen, with synergistic responses to carbon dioxide/pH changes as well. These chemoreceptors are located in the carotid bodies and provide input to the nucleus tractus solitarius. Other central and peripheral receptors include central hypothalamic thermoreceptors, which provide stimulus for respiration in accordance with the energy and metabolic needs of the organism, and peripheral lung mechanoreceptors, which provide input on lung distention and volume and adjust ventilation accordingly.[5]

All these peripheral receptors have inputs on the central respiratory pattern generators, which then communicate with motor neurons that innervate the important respiratory muscles (ie, diaphragm, internal/external intercostals, and abdominal musculature). The central respiratory neurons often have a phase specificity and are active only during a particular portion of the respiratory cycle. For instance,

pre-Bötzinger complex neurons are typically active only during inspiration, whereas those in the retrotrapezoid/parafacial respiratory group are active usually during exhalation.[10] There are other neurons that are active in the third phase (the postinhalation phase) and there are some whose activity spans more than 1 phase.[5]

During sleep, there are changes in the patterns and mechanics of breathing, with some well-described effects depending on the stage of sleep. Typically, during non–rapid eye movement (NREM) sleep, breathing remains regular. Although the rhythmicity remains regular, there is a small decrease in the respiratory rate with an increase in the tidal volume, which leads to an overall decrease in the total minute ventilation.[5] There is an accompanying decrease in the respiratory response to hypercapnia, although the response to hypoxemia is unchanged. This change in carbon dioxide reactivity leads to a small increase in the partial pressure of carbon dioxide levels and a small decrease in blood oxygen levels during sleep. The increase in carbon dioxide levels is also thought to serve as an additional stimulus to compensate for wakefulness-related influences.[5,11] Activity to accessory muscles of respiration and those in the upper airway is often reduced, although this is not thought to significantly alter airway resistance in normal subjects. This loss of muscle activity, however, is thought to be an important contributor to SDB in susceptible patients.

During rapid eye movement (REM) sleep, breathing is no longer regular, and there can be a large breath to breath variability in pattern and tidal volume. Typically, respiratory patterns can become irregular, with rapid increases in inspiratory muscle activity interrupted with short periods of inactivity.[5] Thresholds to hypercapnia, hypoxemia, and arousals are altered during REM sleep, with potential large increases in partial pressures of carbon dioxide and oxygen seen in susceptible individuals. All accessory muscles of respiration are essentially atonic during REM sleep, and the full maintenance of the minute ventilation (and consequently the arterial carbon dioxide and oxygen levels) is dependent on the diaphragm. It is also thought that phasic events during REM, particularly ponto-geniculo-occipital spikes, may be associated with the variability of breathing.

EFFECTS OF NARCOTICS ON BREATHING IN NORMAL INDIVIDUALS

Opioids are a group of naturally occurring and synthetic chemicals that bind to opioid receptors in the body, found primarily in the central nervous system and gastrointestinal tract. More than 1000 members of the receptor family have been reported, and they structurally act like G protein–coupled receptors.[12] Binding of an opioid ligand induces changes in the extracellular domain of the receptor, with transmission of signal through a transmembrane portion into the intracellular component of the receptor, changing it into a guanine nucleotide exchange factor. The receptor associates with a G protein and exchanges guanosine diphosphate for guanosine triphosphate, activating a downstream signaling cascade. This signaling cascade leads to changes in the cell, including opening and closing of various ion channels in the cell. The resultant flux of ions, such as those of calcium and potassium, changes the electrical balance of the cell, with resulting decreased excitability.

Four classes of opioid receptors have been described, including opioid δ receptor (DOP), opioid μ receptor (MOP), nociceptin/orphanin peptide receptor (NOP), and opioid κ receptor (KOP).[12–14] Each receptor has at least 1 associated endogenous ligand, with the overall opioid receptor system mediating physiologic processes including pain, respiration, and stress. All opioid receptor types are typically associated with analgesia, although NOP receptors have been associated with hyperalgesia when stimulated with agonists superspinally.[15] Besides analgesia, stimulation of

opioid receptors is often associated with respiratory depression, particularly with stimulation of MOP and KOP receptors. Synthetic and semisynthetic opioids bind to each receptor with varying degrees of affinity, typically with the greatest affinity for MOP receptors. Ligands may act as pure agonists, mixed agonists/antagonists, or pure antagonists. Exogenous opioids are usually metabolized hepatically, with renal clearance.

With regard to breathing, opioids cause decreases in central respiratory pattern generation with resultant decreases in respiratory rate and/or tidal volume. Much of the previous work in the literature has been performed in animals, with less information available regarding potential mechanisms in humans. In the available animal and human studies, the effects of opioids on breathing have mostly involved 2 types of studies: (1) direct instillation of opioids on chemosensitive areas such as the carotid body or brainstem or (2) systemic administration of opioids in awake and anesthetized humans and animals.[16] When opioid agonists were directly applied to medullary and pontine respiratory associated centers (including the nucleus tractus solitarius), decreases in peak activity were seen, although basal activity did not seem to change.[16,17] Opiates applied to the ventral medullary surface of animals were shown to decrease tidal volume but increase respiratory rate, whereas application to the rostral dorsal pons was shown to decrease respiratory rate.[16,18] Among the neuronal centers important for central respiratory rhythm generation, only pre-Bötzinger complex neurons are sensitive to opioids. Similar findings are also seen with opiates and peripheral chemoreceptors. When morphine was applied to the carotid bodies of anesthetized cats, decreases in chemoreceptor activity were seen that were reversed with application of an opioid antagonist (naloxone).[19]

In studies of systemic administration of opiates, there is limited applicability of animal data to human responses, because there is significant cross-species variability in responses. For instance, systemic administration of opioids in cats or goats produces respiratory stimulation, whereas in humans, opiates produce clear respiratory depression.[16] At lower doses, opiates produce a respiratory depression via reduction in tidal volume that is proportional to the dose and potency of the opiate administered.[20] At higher doses, decreases in respiratory rate and rhythm generation are seen. When morphine was given to normal human subjects, decreases in hypercapnic and hypoxic respiratory drives were also seen.[21] This effect seems to predominantly affect the respiratory response to hypoxemia; at higher doses this response is virtually ablated.[21,22] This response suggests that the action of opioids on hypoxemic respiratory drive is through effects on peripheral chemoreceptors, although a central mechanism of action has been suggested in some studies. In a study of 30 subjects randomly assigned to receive intrathecal morphine, intravenous morphine, or placebo, similar decreases in hypoxemic respiratory drive were seen.[23] Based on these studies, it seems that opiates act not only on central pattern generators but also on chemosensitive receptors that are both centrally located and in the periphery.

Although less well studied, the effects of opioids on other components involved in the control of breathing are important. For instance, there is an increase in respiratory effort in response to an increase in respiratory airway resistance or loading.[16] Administration of opiates has been shown to decrease this compensatory increase in respiratory effort.[22,24] There are also upper airway muscle reflexes that are important in maintaining airway patency. These upper airway muscles (such as the genioglossus muscles) receive tonic input during wakefulness, with phasic increases before inspiration.[25] The activity of these muscles decreases during sleep, although in normal subjects, airway patency and resistance remain essentially unchanged. However, administration of respiratory depressants (including opioids) has been associated

with tendency for obstruction at the upper airway level as well as rigidity of accessory muscles of respiration (ie, intercostals and abdominal muscles). For instance, administration of a highly selective MOP agonist (fentanyl or sufentanil) has been associated not only with decreases in respiratory rate and depth of respiration but also with glottic/supraglottic obstruction.[26,27]

CLINICAL EFFECTS OF NARCOTICS ON BREATHING IN THOSE SUSCEPTIBLE TO SDB

Clinical data looking at the effects of opioids on SDB have typically consisted of case series, studies of patients on long-term oral opioids for malignant and nonmalignant reasons, or studies of patients enrolled in long-term methadone programs. Interpretation across studies is therefore difficult, because patients on long-term opioids are often concurrently prescribed antidepressants and benzodiazepines, both of which have been described to alter respiratory patterns. In a small study of 12 normal subjects, acute administration of a short-acting oral narcotic did not seem to be associated with the development of any SDB.[28] Nevertheless, a growing body of literature has described several consistent clinical findings in patients on long-term opioid therapy. Each of these findings is now examined in detail and the supporting literature is described.

Development of Central Apnea During Sleep

A significant proportion of patients taking long-term opioids develop central apnea during sleep and this seems to be a consistent finding. In one of the earliest studies, Teichtahl and colleagues[29] examined 10 patients in a methadone maintenance program and performed a clinical assessment and overnight polysomnography. They found that all 10 patients had evidence of central sleep apnea, with 6 patients having a central apnea index (CAI) greater than 5 and 4 patients with a CAI greater than 10. In a larger follow-up study of 50 patients taking long-term methadone, 30% of the patients had a CAI greater than 5, and 20% had a CAI greater than 10.[30] All the patients had been on stable doses of methadone for at least 2 months, and other potentially contributing diagnoses (such as congestive heart failure) had been excluded. Similar findings have also been described for opioids other than methadone. In 2 studies of patients enrolled in a chronic pain clinic and had been receiving a variety of opiate medications (including methadone), the investigators noted that approximately 25% of patients showed evidence of central sleep apnea, with a CAI greater than 5.[31,32]

The mechanism underlying the presence of significant central sleep apnea is not clear. Although the opioids have been presumed to be the primary culprit through their action on central respiratory pacemakers and chemoreceptors, it is not clear if excessive dosing is the only responsible mechanism. When blood toxicology tests were examined in a group of patients on long-term methadone maintenance, serum methadone levels did seem to be the most significant item correlated to the severity of central sleep apnea.[30] However, in multivariate analyses, the serum methadone level contributed to only 12% of the variance of the severity of central sleep apnea. The investigators suggested various mechanisms contributing to central sleep apnea, including prior structural damage from illicit drug use, disrupted hypoxic/hypercapnic respiratory responses, and contributions from the concurrent use of antidepressants and benzodiazepines. In a study of 50 patients receiving long-term methadone therapy, the investigators found significant decreases in the respiratory response to hypercapnia and increased ventilatory responses to hypoxia. Twenty percent of the patients had evidence of carbon dioxide retention while awake (defined as

$Paco_2$>45), and approximately 30% had an increased alveolar-arterial oxygen gradient.[33] These ventilatory changes also seemed to be manifested through alterations in the respiratory rate and not through changes in the tidal volume.

Development of Ataxic Breathing During Sleep

Other clinical findings include the development of irregular breathing patterns in patients receiving long-term opioid therapy. In a case series of three patients receiving a variety of opiate medications, irregular breathing patterns were described, consisting of irregular respiratory pauses and gasping without periodicity, found primarily during non-REM sleep.[34] The authors felt the breathing was consistent with ataxic or Biot breathing, previously described in patients with acute neurologic disease. This pattern of breathing was first described in 1876 by Camille Biot, a French physician, in a child with tuberculous meningitis.[35] He described a respiratory pattern with pauses, distinct from Cheyne-Stokes respiration, called ''rhythme meningitique.'' This pattern of respiration has been described for patients on opioids, who have an erratic variability in the respiratory rate and effort of breath with frequent irregular breathing. In a study of 60 patients receiving long-term opioid therapy, more than 70% of patient on opiates were observed to have ataxic or Biot breathing, compared with 5% of controls in an age- and sex-matched group.[36] This irregular breathing seemed to be related to dosing of opiates; more than 90% of subjects on a morphine dose equivalent to greater than 200 mg daily were noted to have evidence of Biot breathing.

Development of Obstructive Apneas or Hypopneas During Sleep

There does not seem to be a clear consensus in the literature regarding the development of obstructive sleep apnea syndrome in patients who receive long-term opiate treatment. As noted earlier, acute administration of an oral narcotic was not associated with increases in obstructive apneas or hypopneas in normal subjects.[28] Concurrent evaluation of upper airway function in these subjects did not find any increase in pharyngeal airway resistance while awake, although decreases in ventilatory responses to hypoxia were seen. Another case series of 3 patients noted only modest increases in the obstructive apnea and hypopnea index (AHI) in 2 patients, 1 of whom had a diagnosis of obstructive sleep apnea before being prescribed previous opiate therapy.[37] In a study of 50 subjects on long-term methadone therapy, no statistically significant increases in the occurrence of obstructive sleep apnea compared with a control group were seen.[30] In contrast, Farney and colleagues[34] described 3 patients on long-term sustained-release opioid medications with markedly prolonged obstructive hypopneas during sleep, each lasting greater than 5 minutes on average. These obstructive hypopneas were associated with severe oxyhemoglobin desaturations and seen exclusively during NREM sleep. Another 2 case series of 6 and 10 subjects, respectively, noted that obstructive respiratory events accounted for between 16% and 80% of the increase in the AHI.[29,38] A recent study of 71 patients on long-term methadone maintenance therapy with subjective sleep complaints noted that 35% of the study population had evidence of obstructive sleep apnea on an overnight home polysomnogram. The investigators did not observe significant central sleep apnea in their cohort, with approximately 15% of subjects having a CAI greater than 5. When methadone levels and concurrent drug use were tested, neither seemed to be correlated with the degree of central sleep apnea. In 2 separate studies from the same pain clinic, 35% and 57% of the subjects had evidence of either pure or mixed obstructive sleep apnea.[31,32] The degree of SDB correlated most with the dose of methadone in statistical analyses, although the investigators did not specifically look at obstructive versus central events during sleep.

Development of Hypoxemia

Hypoxemia in patients taking long-term opioids has been variably described in the literature, with many groups reporting an increased incidence of significant oxyhemoglobin desaturation during sleep among patients receiving long-term opioid therapy compared with control groups.[29,31,36] The increase in nocturnal hypoxemia, however, is not entirely explained by a concurrent increase in SDB. In a study of 98 patients on long-term opioid medications, 72% had evidence of nocturnal oxyhemoglobin desaturation, defined as an arterial oxyhemoglobin saturation during sleep of (1) less than 90% for 5 minutes with a nadir of 85% or less or (2) greater than 30% of the total sleep time.[31] Ten percent of the subjects with significant nocturnal desaturations did not have evidence of sleep apnea on overnight polysomnography. When the investigators examined for the incidence of significant desaturations during sleep among subjects with varying degrees of SDB, they found only a moderate increase in the incidence of sleep-associated desaturations with increased SDB severity (60% in subjects with an AHI in the mild range vs 80% of subjects with an AHI in the moderate to severe range). There was a statistically significant correlation, albeit a weak one, between the morphine equivalent dose and the time spent in sleep with an oxyhemoglobin saturation less than 90% ($R = .237$, $P = .023$). Ten percent of the subjects also had evidence of hypoxemia during wakefulness that worsened during sleep. Similar findings were seen in a study of 60 patients on long-term opioid use, with a statistically significant difference in average arterial oxygen saturation in awake subjects compared with a control group.[36]

EFFECTS OF NARCOTICS ON SLEEP ARCHITECTURE

Not much is known about the effects of opioids on sleep architecture. Early studies in animals have demonstrated disruption in sleep associated with opioid administration, including decreases in total sleep time and REM sleep.[39] More recent studies in human subjects have primarily demonstrated decreases in slow wave and REM sleep, with concurrent increases in stage 2 sleep.[40] Similar findings were also noted in a study of 42 subjects who were administered a one-time dose of either extended-release morphine or methadone.[41] Another study in patients who underwent abdominal surgery and subsequently received narcotics for pain relief reported an absence of REM sleep for the first few nights, with a large rebound in REM sleep later in their convalescence.[42] Others have found a suggestion of increased nocturnal arousals in patients on long-term opioids, albeit measured via limb electromyogram.[43] It seems that the changes in REM and slow wave sleep are the most consistent, although a significant amount of variability in the findings remains. In addition, most of the studies available in the literature consist of case series, without accompanying control groups. Many of the previous studies have also relied on abnormal subjects for the studies, specifically previous narcotic addicts, as the study population. Such a focus limits the interpretation of these studies as well as issues such as variability in scoring of sleep studies, doses of opioids used, and types of narcotics used (ie, short- vs long-acting). More work is necessary to further delineate the changes in sleep architecture with opioid medications.

TREATMENT

Currently, there is no clear consensus on the treatment of opioid-associated SDB. As noted earlier, patients may have several disturbances in their respiratory patterns during sleep, including characteristics of central sleep apnea, obstructive sleep

apnea, ataxic breathing, or a combination of all 3 types. Several nocturnal ventilatory strategies have been tried with varying degrees of success, including continuous positive airway pressure (CPAP) support, bilevel therapy (usually with a backup rate), and adaptoservo ventilation (ASV). In the case series of 3 patients on long-term opioid medication with evidence of sleep-disordered breathing discussed earlier, the investigators attempted titration with CPAP therapy with limited success.[34] Although the number of respiratory events decreased, the patients were reported to have continued severe hypoxemia that necessitated supplemental oxygen. Despite relative tolerance of increasing CPAP pressures, the patients continued to have a large number of central respiratory events, and there was some suggestion that the CPAP may have worsened the central sleep apnea. Similar findings were reported in another case series of 6 patients on long-term methadone maintenance.[38] Five of the 6 subjects agreed to proceed with a CPAP titration, and in 4 of these subjects, significant central apneas persisted despite titration up to a CPAP pressure of 20 cm H_2O. In 1 subject, it seemed that the CPAP was effective at a pressure of 20 cm H_2O, although the patient was unable to tolerate therapy. Two case series of 5 and 22 patients on long-term opioids with SDB noted increases in the CAI with CPAP treatment, with an average increase of 10 to 20 central events per hour.[34,44] Although CPAP may be beneficial in relieving the airway obstruction potentially associated with opioid use, it does not seem to be able to successfully treat any concurrent central sleep apnea and may be associated with increased frequency of central apneas during sleep.

Bilevel therapy with a backup rate has also been suggested as a treatment for patients with mixed central and obstructive sleep apnea, although there have not been many studies published on the subject. In the case series reported by Alatarr and colleagues,[38] patients who failed CPAP therapy because of efficacy or tolerance issues were then offered a bilevel titration, with timed backup rates of 12 to 16. Four patients agreed to proceed and were successfully titrated, with subsequent improvement in reports of daytime sleepiness. Three of these 4 patients required supplemental oxygen despite a successful titration. Bilevel therapy has been examined in patients with mixed obstructive and central sleep apnea as well as obesity hypoventilation syndromes with some success, although there are no comparisons available on the use of bilevel therapy and other modalities (such as CPAP or ASV) in patients with opioid-associated SDB.[45–49] However, the authors have completed work on an unpublished study on more than 40 patients with a combination of obstructive sleep apnea and long-term opioid intake. Bilevel therapy with a backup rate was successful in controlling all patients with a 6 months follow-up compared with CPAP (Christian Guilleminault, unpublished data, 2010).

There has been growing interest in the use of ASV pressure support as a new modality in the treatment of SDB in patients receiving long-term opioid treatment. ASV machines work by varying the amount of ventilatory support, with the goal of avoiding hyperventilation and keeping the patient's partial pressure of carbon dioxide above the apneic threshold. These machines typically operate using an algorithm that measures the patient's minute ventilation on a running and spontaneous basis. Pressure support is adjusted dynamically to decrease in times of increased patient respiratory effort and increase during times of decreased patient respiratory effort. There has been a growing literature examining their use in Cheyne-Stokes respiration, central sleep apnea, and mixed obstructive/central sleep apnea syndromes with positive results.[50–54] Two case series have examined the use of ASV in patients on long-term opioid therapy with conflicting results. Javaheri and colleagues[44] examined 5 consecutive patients referred for an evaluation for obstructive sleep apnea who

were also concurrently taking long-term opioid medication. All patients underwent an overnight diagnostic polysomnogram followed by a CPAP titration. CPAP was found to be an ineffective therapy in all patients, and they underwent a third night study with titration with ASV. The average AHI decreased from 70 to 20 with ASV; the remainder consisted entirely of hypopneas. The CAI, which had increased with CPAP therapy (from 26 to 37), was 0 at the end of the ASV titration. In contrast, Farney and colleagues[55] performed a retrospective analysis of 22 patients on long-term opioid use who were referred for SDB and had been tested with ASV. The average AHI decreased from 66.6 at baseline to 54.2 with ASV but was not statistically significant. Although the obstructive apnea index decreased significantly, the hypopnea index was observed to increase. There was no statistically significant change in the CAI, and the investigators noted that ataxic breathing continued. Unlike in the study by Javaheri and colleagues,[44] the end expiratory pressure was not titrated in the subjects in the study by Farney and colleagues,[55] suggesting a possible rationale for the relatively ineffective control of obstructive events in their study. Further research is necessary to determine the role of ASV in the treatment of opioid-associated SDB.

SUMMARY

The use of opioid medication is increasing with the potential for adverse effects on respiration, especially during sleep. Opioids seem to affect the control of breathing on many levels, including alterations in the central respiratory pacemaker function as well as effects on central and peripheral chemoreceptors. The use of opioids has been associated with abnormal breathing patterns in susceptible patients, including development of central sleep apnea, obstructive sleep apnea, ataxic breathing, and hypoxemia. The optimal treatment for these patients with opioid-associated SDB is not well-known, although equipment using positive-airway-pressure during sleep clearly provides benefit to these subjects. Further work is necessary to elucidate the mechanisms of SDB in patients on long-term opioid medication as well as how best to treat them.

REFERENCES

1. Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med 2003;349: 1943.
2. Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage 1996;11:203.
3. Gilson AM, Ryan KM, Joranson DE, et al. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997–2002. J Pain Symptom Manage 2004;28(2):176–88.
4. Joranson DE, Ryan KM, Gilson AM, et al. Trends in medical use and abuse of opioid analgesics. JAMA 2000;283(13):1710–4.
5. Kubin L. Respiratory physiology: CNS ventilatory control. In: Opp MR, Kilduff TS, Armitage R, et al, editors. SRS basic of sleep guide, 1st edition. Westchester (IL): Sleep Research Society; 2005. p. 81–8.
6. McKay LC, Feldman JL. Unilateral ablation of pre-Bötzinger complex disrupts breathing during sleep but not wakefulness. Am J Respir Crit Care Med 2008; 178:89–95.
7. McKay LC, Janczewski WA, Feldman JL. Sleep-disordered breathing after targeted ablation of pre Bötzinger complex neurons. Nat Neurosci 2005;8:1142–4.

8. Janczewski WA, Feldman JL. Distinct rhythm generators for inspiration and expiration in the juvenile rat. J Physiol 2006;570(Pt 2):407–20.
9. Onimaru H, Homma I. A novel functional group for respiratory rhythm generation in the ventral medulla. J Neurosci 2003;23:1426–78.
10. Walker JM, Farney RJ. Are opioids associated with sleep apnea? A review of the evidence. Curr Pain Headache Rep 2009;13(2):120–6.
11. Feldman JL, Mitchell GS, Nattie EE. Breathing: rhythmicity, plasticity, chemosensitivity. Annu Rev Neurosci 2003;26:239–66.
12. Martin TJ, Eisenach JC. Pharmacology of opioid and nonopioid analgesics in chronic pain states. J Pharmacol Exp Ther 2001;299(3):811–7.
13. Inturrisi CE. Clinical pharmacology of opioids for pain. Clin J Pain 2002;18:S2–13.
14. Pattinson KT. Opioids and the control of respiration. Br J Anaesth 2008;100:747–58.
15. Lambert DG. The nociceptin/orphanin FQ receptor: a target with broad therapeutic potential. Nat Rev Drug Discov 2008;7(8):694–710.
16. Santiago TV, Edelman NH. Opioids and breathing. J Appl Physiol 1985;59(6): 1675–85.
17. Denavit-Saubié M, Champagnat J, Zieglgänsberger W. Effects of opiates and methionine-enkephalin on pontine and bulbar respiratory neurones of the cat. Brain Res 1978;155(1):55–67.
18. Pokorski M, Grieb P, Wideman J. Opiate system influences central respiratory chemosensors. Brain Res 1981;211(1):221–6.
19. McQueen DS, Ribeiro JA. Inhibitory actions of methionine-enkephalin and morphine on the cat carotid chemoreceptors. Br J Pharmacol 1980;71(1): 297–305.
20. Eckenhofff JE, Oech R. The effects of narcotics and antagonists upon respiration and circulation in man. Clin Pharmacol Ther 1960;1:483–524.
21. Weil JV, McCullough RE, Kline JS, et al. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. N Engl J Med 1975; 292:1103–6.
22. Kryger MH, Yacoub O, Dosman J, et al. Effect of meperidine on occlusion pressure responses to hypercapnia and hypoxia with and without external inspiratory resistance. Am Rev Respir Dis 1976;114:333–40.
23. Bailey PL, Lu JK, Pace NL, et al. Effects of intrathecal morphine on the ventilatory response to hypoxia. N Engl J Med 2000;343(17):1228–34.
24. Santiago TV, Goldblatt K, Winters A, et al. Respiratory consequences of methadone: the response to added resistance to breathing. Am Rev Respir Dis 1980; 122:623–8.
25. Remmers JE, DeGroot WJ, Sauerland EK, et al. Pathogenesis of upper airway occlusion during sleep. J Appl Physiol 1978;44:931–8.
26. Drummond GB. Comparison of decreases in ventilation caused by enflurane and fentanyl during anaesthesia. Br J Anaesth 1984;55:825–35.
27. Bennett JA, Abrams JT, Van Riper DF, et al. Difficult or impossible ventilation after sufenidil-induced anaesthesia is caused primarily by vocal cord closure. Anesthesiology 1997;87:1070–4.
28. Robinson RW, Zwillich CW, Bixler EO, et al. Effects of oral narcotics on sleep-disordered breathing in healthy adults. Chest 1987;91:197–203.
29. Teichtahl H, Prodromidis A, Miller B, et al. Sleep-disordered breathing in stable methadone programme patients: a pilot study. Addiction 2001;96(3): 395–403.
30. Wang D, Teichtahl H, Drummer O, et al. Central sleep apnea in stable methadone maintenance treatment patients. Chest 2005;128(3):1348–56.

31. Mogri M, Desai H, Webster L, et al. Hypoxemia in patients on chronic opiate therapy with and without sleep apnea. Sleep Breath 2009;13(1): 49–57.
32. Webster LR, Choi Y, Desai H, et al. Sleep-disordered breathing and chronic opioid therapy. Pain Med 2008;9(4):425–32.
33. Teichtahl H, Wang D, Cunnington D, et al. Ventilatory responses to hypoxia and hypercapnia in stable methadone maintenance treatment patients. Chest 2005; 128(3):1339–47.
34. Farney RJ, Walker JM, Cloward TV, et al. Sleep-disordered breathing associated with long-term opioid therapy. Chest 2003;123(2):632–9.
35. Biot MC. Contribution a l'etude du phenomene respiratoire de Cheyne-Stokes. Lyon Med 1876;23:517–28 561–7 [in French].
36. Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. J Clin Sleep Med 2007;3(5):455–61.
37. Mogri M, Khan MI, Grant BJ, et al. Central sleep apnea induced by acute ingestion of opioids. Chest 2008;133:1484–8.
38. Alattar MA, Scharf SM. Opioid-associated central sleep apnea: a case series. Sleep Breath 2009;13(2):201–6.
39. Nash P, Colasanti B, Khazan N. Long-term effects of morphine on the electroencephalogram and behavior of the rat. Psychopharmacologia 1973;29(3): 271–6.
40. Shaw IR, Lavigne G, Mayer P, et al. Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: a preliminary study. Sleep 2005;28(6):677–82.
41. Dimsdale JE, Norman D, DeJardin D, et al. The effect of opioids on sleep architecture. J Clin Sleep Med 2007;3(1):33–6.
42. Knill RL, Moote CA, Skinner MI, et al. Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. Anesthesiology 1990; 73(1):52–61.
43. Staedt J, Wassmuth F, Stoppe G, et al. Effects of chronic treatment with methadone and naltrexone on sleep in addicts. Eur Arch Psychiatry Clin Neurosci 1996;246(6):305–9.
44. Javaheri S, Malik A, Smith J, et al. Adaptive pressure support servoventilation: a novel treatment for sleep apnea associated with use of opioids. J Clin Sleep Med 2008;4(4):305–10.
45. Kushida CA, Chediak A, Berry RB, et al. Positive Airway Pressure Titration Task Force, American Academy of Sleep Medicine. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med 2008;4(2):157–71.
46. Kuźniar TJ, Morgenthaler TI. Treatment of complex sleep apnea syndrome. Curr Treat Options Neurol 2008;10(5):336–41.
47. Ogawa A, Iwase T, Yamamoto T, et al. Improvement of Cheyne-Stokes respiration, central sleep apnea and congestive heart failure by noninvasive bilevel positive pressure and medical treatment. Circ J 2004;68(9):878–82.
48. Arzt M, Wensel R, Montalvan S, et al. Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure. Chest 2008; 134(1):61–6.
49. Fietze I, Blau A, Glos M, et al. Bi-level positive pressure ventilation and adaptive servo ventilation in patients with heart failure and Cheyne-Stokes respiration. Sleep Med 2008;9(6):652–9.

50. Teschler H, Döhring J, Wang YM, et al. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. Am J Respir Crit Care Med 2001;164(4):614–9.
51. Randerath WJ, Galetke W, Kenter M, et al. Combined adaptive servo-ventilation and automatic positive airway pressure (anticyclic modulated ventilation) in co-existing obstructive and central sleep apnea syndrome and periodic breathing. Sleep Med 2009;10(8):898–903.
52. Randerath WJ, Galetke W, Stieglitz S, et al. Adaptive servo-ventilation in patients with coexisting obstructive sleep apnoea/hypopnoea and Cheyne-Stokes respiration. Sleep Med 2008;9(8):823–30.
53. Banno K, Okamura K, Kryger MH. Adaptive servo-ventilation in patients with idiopathic Cheyne-Stokes breathing. J Clin Sleep Med 2006;2(2):181–6.
54. Szollosi I, O'Driscoll DM, Dayer MJ, et al. Adaptive servo-ventilation and deadspace: effects on central sleep apnoea. J Sleep Res 2006;15(2):199–205.
55. Farney RJ, Walker JM, Boyle KM, et al. Adaptive servoventilation (ASV) in patients with sleep disordered breathing associated with chronic opioid medications for non-malignant pain. J Clin Sleep Med 2008;4(4):311–9.