HHS Public Access

Author manuscript

Pain Med. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Pain Med. 2015 October ; 16(0 1): S22–S26. doi:10.1111/pme.12910.

Opioid Therapy and Sleep Disorders: Risks and Mitigation Strategies

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Abstract

Objective—Patients with chronic pain frequently experience concomitant sleep disorders. There has been controversy on whether opioids have a beneficial or deleterious effect on sleep quality, duration and efficiency. There is also concern regarding the association between chronic opioid therapy and sleep disordered breathing and the increased risk for unintentional opioid related overdose. This article provides a narrative review of the literature on the effect of opioids on sleep disorders and discusses risk assessment and mitigation strategies.

Design—A narrative review of the current literature on the effect of prescription opioids on sleep quality and efficiency, the relationship between opioids and sleep disorders and potential risk factors in patients with chronic pain.

Results—There is conflicting evidence regarding the benefit of opioids in improving sleep quality, duration and efficiency with several studies and reviews suggesting a beneficial effect of opioids on sleep and other studies demonstrating the opioids can cause sleep disturbance leading to hyperalgesia. There was credible evidence of a strong relationship between opioids and sleep disordered breathing with noted risk factors including use of methadone, high opioid dosing (> 200 mg MED) and combining opioids with benzodiazepines.

Conclusions—Further research is required to elucidate the effect of prescription opioids on sleep quality and pain intensity and the risks associated with opioids and sleep disordered breathing. The risk of sleep disordered breathing should be routinely assessed in patients on chronic opioid therapy.

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Conflicts of Interest: MDC has received honoraria, grant support, consultant fees and/or travel expenses from the following companies: Cordant Healthcare, Campbell Alliance, Zogenix, Nektar LRW has received honoraria, consultant fees and/or travel expenses from the following companies: AcelRx Pharmaceuticals, Acura Pharmaceuticals, AstraZeneca, BioDelivery Sciences International, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Cara Therapeutics, Charleston Labs, Collegium Pharmaceuticals, CVS Caremark, Depomed, Egalet, Grunenthal USA, Inspirion Pharmaceuticals, Insys Therapeutics, Jazz Pharmaceuticals, Kaleo, Mallinckrodt, Medtronic, Nektar Therapeutics, Neura Therapeutik, Nevro Corporation, Orexo Pharmaceuticals, Pfizer, Proove Biosciences, QRx Pharma, Quintiles, Shionogi, Signature Therapeutics, TEVA, Theravance, Trevena, Zogenix.

Keywords

Opioid therapy; chronic pain; sleep disordered breathing; methadone

Introduction

Opioid therapy has been a major component of comprehensive pain treatment for patients with chronic noncancer pain (CNCP). There has been recent debate regarding the efficacy and safety of long-term opioid therapy, particularly given the burgeoning prevalence of opioid-related overdoses.[1-4] It has been accepted practice that patients who are on chronic opioid therapy (COT) (continuous use greater than 90 days) be placed on a regimen of a long-acting opioid preparation with access to short-acting opioids for breakthrough pain. This has promoted patients being maintained on around the clock opioids at relatively high dosages. While many patients benefit from opioid therapy without experiencing significant adverse effects, there is a subgroup of patients that can develop a variety of minor to major adverse effects including bladder dysfunction, pruritis, opioid-induced constipation, cardiac side effects, hormonal changes, cognitive difficulties, sedation, addiction and sleep disorders. [5]

Pain and Sleep disorders

The majority of patients with CNCP report difficulties with some type of sleep disturbance, with prevalence of sleep disorders estimated as greater than 50% in this patient population.[6-9] Patients with chronic pain who report significant sleep disturbance endorse higher rates of depression and anxiety as well as greater pain intensities. [10-11] Studies have demonstrated a bidirectional relationship between pain and sleep; poorly controlled chronic pain can reduce sleep quality and conversely poor sleep quality can increase pain intensity.[11-15] While the origin of sleep disturbance may include poorly controlled pain, in a number of patients, these sleep disorders can be attributable to the use of opioids. Additionally, there is significant evidence of the deleterious effect of opioids on sleep disordered breathing (SDB), which can increase the risk of unintentional overdose.

This article will review the literature on the effects of opioids on sleep quality and efficiency and the increased risk of SDB and unintentional overdoses with COT. Risk assessment and mitigation strategies will be discussed.

Opioids and Sleep Quality and Efficiency

There are conflicting reports on the effect of opioids on sleep quality and efficiency. A 2009 narrative review of the literature was conducted on the potential efficacy of analgesia in improving pain-related sleep disorders.[16] A number of studies were identified that demonstrated subjective improvement in sleep quality, including increased duration of sleep and diminished need for sleep medication, improvement in sleep onset insomnia, and terminal insomnia with the use of long-acting opioids. For example, one study cited was a randomized, placebo-controlled, double-blind, 4 week trial followed by an open label, 26-week extension study, evaluating the efficacy of a once per day dosing of extended release

morphine sulfate (ERMS). During the 4 week double blind phase subjects were randomized into a once daily ERMS 30 mg taken every am, once daily ERMS 30 mg taken very pm, twice-daily ERMS 15 mg or placebo group. In the extension, open-label trial, subjects received either once daily ERMS every am or every pm, allowing for dose titration to maximize analgesia. Subjects in the double-blind portion of the trial who achieved adequate pain control with a once daily dosing of ERMS, taken either a.m. or p.m., had a statistically significant improvement in sleep quality as compared to the twice-daily regimen and placebo. This was also associated with significant improvement in sleep duration, an improvement in ability to initiate sleep and a reduced need for sleep medication preparations when compared with placebo.[17] The authors of the review cited several other randomized control trials that had similar results indicating improved sleep quality and efficiency with opioid therapy to control pain. They concluded that improved pain control with appropriate pharmacotherapy, including opioids, may improve sleep quality in patients with CNCP, but cautioned that there is also associated risk of sleep apnea.

In contrast to these findings, there have been other studies that suggest that opioids may cause inhibition of rapid eye movement (REM) and non-rapid eye movement (non-REM) phases of sleep[18,19] which could contribute to exacerbation of pain.[20,21] Shaw et al[18] evaluated seven healthy, pain-free patients with no history of substance use disorder (SUD) that were randomly assigned to an untreated (baseline) condition, intravenous injection of morphine condition or a placebo condition which was an intravenous injection of saline. Standard polysomnographic sleep and respiratory variables were measured and it was discovered that individuals in the morphine group had a reduced duration of slow-wave sleep and moderate reduction in REM sleep. These findings are relevant as there has been evidence that reduction in sleep time and REM can produce hyperalgesia. For example, Roehrs et al [20] evaluated healthy, pain-free, normal sleepers and induced sleep loss (8 hours time-in-bed, 4 hours time-in-bed and 0 hours time in bed) in 7 subjects and REM sleep loss (8 hours time-in-bed, 2 hours time-in-bed, REM deprivation, and non-REM yoked-control conditions in 6 subjects. Pain tolerance was measured using a finger-withdrawal latency to a radiant heat stimulus procedure. They found that finger-withdrawal latency was reduced by 25% in the sleep loss group, and that REM sleep deprivation relative to non-REM yoked control sleep interruption condition reduced finger-withdrawal latency by 32%. They concluded that loss of four hours of sleep and specific REM sleep loss produced hyperalgesia the following day, suggesting that clinical conditions that reduce REM sleep (opioids) may increase pain.

Anecdotally, many patients will use opioids at night to improve their sleep quality, but additional research is needed to tease apart the effect of opioids on sleep structure, efficacy and pain.

Opioids and Sleep Disordered Breathing

There has been an alarming increase in unintentional overdose fatalities which has prompted increased scrutiny about the practice of opioid therapy; in particular, extended release and/or high dosing of opioids in patients with CNCP. The causes of overdoses are typically multifactorial in nature and can include starting a patient on too high of a dose, particularly

in opioid naïve patients; rapid opioid dose escalation; combining opioids with benzodiazepines; an overreliance on the use of conversation tables; non-adherence by patients to either control their pain to cope with co-occurring psychological disorders or undetected SUD; and, lastly, unanticipated comorbidities including undetected QT prolongation with methadone, and sleep disordered breathing (SDB).[22]

A number of studies have evaluated the relationship between COT and SDB. A study by Mogri et al[23] performed a retrospective analysis of 98 consecutive patients who were receiving COT referred for a polysomnogram. Of the 98 patients, 36% (95% CI, 26-46%) had obstructive sleep apnea (OSA); 24% (95% CI, 16-33%) had central sleep apnea (CSA); 21% (95% CI, 14-31%) had combined OSA and CSA; 4% (95% CI, 0-10%) sleep apnea was classified as indeterminate; and 15% (95% CI, 9-24%) had no sleep apnea. The authors concluded that patients with chronic pain on COT had a high prevalence of sleep apnea and nocturnal hypoxemia. Correa et al[24] conducted a literature review of the prevalence and mechanisms of CSA in patients on COT. Eight quality studies were identified with a combined sample of 560 subjects. The prevalence of CSA in this patient population was 24%. The risk factors for CSA severity in patients on COT included a daily morphine equivalent dose (MED) > 200 mg, low or normal body mass index and combining of opioids and benzodiazepines or hypnotics. In examining treatments to address the SDB, studies revealed that continuous positive airway pressure was most likely ineffective in addressing CSA and could also increase CSA. Walker et al[25] performed a retrospective cohort study examining 60 patients receiving COT matched on age, sex and BMI with 60 patients not on opioids to examine the effect of MED on breathing patterns during sleep. Results indicated that the apneahypopnea index (AHI) was greater in the opioid group (43.5 per hour versus 30.2 per hour, $p < .05$) as a result of increased CSA. Arterial oxygen saturation in the opioid group was significantly lower for both wakefulness and non-REM sleep, but not during REM sleep as compared to the non-opioid group. After controlling for BMI, age and sex, there was a significant dose response relationship between MED and apnea-hypopnea ($p < .001$), obstructive apnea ($p < .001$), hypopnea ($p < .001$) and central apnea indexes ($p < .001$). Ataxic breathing was seen in 92% of the patients receiving an MED dose of 200 mg or higher and in 61% of those patients taking a dose less than 200 mg MED. These results confirm previous results that there was a dose dependent relationship between COT and the development of CSA and ataxic breathing.

In summary there is a robust literature establishing a strong relationship between COT and SDB, which could increase the risk of unintentional opioid related overdoses. Methadone is particularly problematic.

Methadone and Sleep Disorder Breathing

Methadone has been used for the treatment of CNCP and neuropathic pain due to its unique effect at the mu opioid receptor and the N-methyl-d-aspartate (NMDA) receptor. While clinically efficacious, methadone has properties that are especially concerning regarding risk of unintentional overdose due in part to its effect on SDB.

In a study by Webster et al,[26] 147 patients prescribed around-the-clock opioid therapy for at least six months completed a polysomnogram. Outcome measures included the AHI to

assess the overall severity of sleep apnea. The AHI was abnormal in 75% of the patients (39% OSA, 24% CSA, 8% had both OSA and CSA and 4% had sleep apnea of indeterminate type). There was a direct relationship between the AHI and the daily dosage of methadone but not to other classes of around-the-clock opioids. A dosing of 50 mg of methadone was associated with SDB. It was also discovered that there was a direct relationship between the Central Apnea Index (CAI) and the daily dosage of methadone as well as with benzodiazepines. These results suggest that SDB is extremely common in patients with CNCP prescribed COT and that clinicians need to be more cognizant of the dose response relationship with sleep apnea to methadone and benzodiazepines.

Similar results were obtained in a sample of patients receiving methadone maintenance therapy (MMT). A cohort of 71 opioid-dependent patients in MMT for at least three months and complaining of sleep disturbance were evaluated with a home polysomnogram. OSA was discovered in 35.2% of the study population and was associated with higher BMI and longer duration of receiving MMT. CSA was discovered in 14.1% of the sample and was not associated with a methadone dose or concomitant drug use. The authors concluded that SDB was common in patients on MMT, and OSA was more common than CSA.[27]

Risk Assessment and Mitigation Strategies

Clinicians prescribing opioids for CNCP should be knowledgeable of the potential risk factors associated with opioids, SDB and overdoses, and risk assessment and mitigation strategies.

Risk Factors

A number of risk factors associated with opioids and SDB have been identified. General risk factors related to opioids include type of opioid (methadone),[26,27] dosing (> 200mg MED),[24,25] and concomitant use of benzodiazepines and hypnotics. [24,26] Risk factors relative to OSA include elevated BMI, neck circumference (thicker), smoking, nasal congestion, age (> 60 years old), gender (male), family history, and narrowed pathway. Risk factors specific to CSA include h/o stroke or brain tumor, male gender, heart disorders and age (> 65 years old).

Risk Assessment

Risk assessment begins with taking a thorough history and performing a physical examination including assessing neck circumference and evaluating throat and nose for restricted airway. For completeness review medical records and obtain a baseline urine drug test to assess for non-prescribed benzodiazepines or other CNS depressants. If the patient is at risk for SDB and is on COT or is being considered for opioid therapy a polysomnogram (portable at home or in a sleep lab) should be considered especially if methadone is being prescribed.

Risk Mitigation

If SDB is suspected or confirmed and the patient is being prescribed COT, one should consider a number of risk mitigation interventions including:

- Opioid dose reduction
- Trial of non-opioid therapies (NSAIDs, antiepileptic drugs, physical therapy, antidepressants etc) in lieu of opioids
- Avoiding use of benzodiazepines, sedatives, hypnotics
- Caution against alcohol use
- Sleep medicine consultation and treatment of SDB (for example there is evidence of the efficacy of adaptive cervo-ventilation and bi-level positive airway pressure ventilation for CSA in patients on COT[28])

Conclusions

There is persuasive evidence that SDB (OSA, CSA and mixed OSA and CSA) is common in patients receiving COT and that there is a strong relationship between SDB and risk for unintentional opioid related mortality and morbidity. A number of risk factors for the development of SDB in this patient population have been postulated but additional research is needed to further our understanding of the association between dosing, class and type (long-acting versus short acting preparation) of opioids and SDB and risk of opioid-related overdose fatalities. Although there is strong evidence of a dose-dependent relationship between COT and SDB. Further research is also warranted on the deleterious verses the beneficial effect of opioids on sleep quality and efficiency. Clinicians should be judicious in prescribing opioids in a patient at risk for having SDB especially at high doses and if other CNS depressants are being prescribed. Risk assessment of SDB in patients on COT should be ongoing and dynamic as certain conditions may change over time (BMI, prescription of benzodiazepines by another clinician, changes in health habits etc.). Lastly, there is little evidence supporting the notion that COT is safe as patients become tolerant of the respiratory depressive effects of opioids.[25]

Acknowledgments

MDC and LRW would like to acknowledge the support from Grant 1R01DA032776-01 from the National Institute on Drug Abuse, National Institutes of Health in the writing of this manuscript.

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