

Can pharmacological and non-pharmacological sleep aids reduce post-operative pain and opioid usage? A review of the literature

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Abstract

Sleep is important for our health and well-being and is especially pertinent to orthopedic surgery because it has been shown to play a role in pain tolerance. Knowing the benefits of sleep, one way to positively impact patients' pain and recovery post-surgery is to encourage sleep. Zolpidem, a pharmacologic sleep aid, has been shown to decrease opioid consumption, reduce pain, and increase quality of life when briefly used after orthopedic procedures. Cognitive Behavioral Therapy for Insomnia (CBT-I), a nonpharmacologic sleep aid, has been shown to increase the quality of sleep and sleep time, decrease sleep onset latency, decrease pain, and help patients maintain those gains. Because of the dangers of opioids, it is important for physicians to search for alternative methods to manage their patients' pain, like zolpidem and CBT-I. More research is needed to determine which method may be the most efficacious and how these can be integrated into patient care.

Introduction

Sleep confers far ranging health benefits from increased pain tolerance and healing, to improved cardiovascular health, consolidated memories, and an improved immune system.¹ Studies have shown that patients have profound sleep disturbances due to pain and discomfort after surgery.² Patients who underwent total hip (THA) and total knee (TKA) arthroplasties were found to have an average loss of 1.5 days of sleep after surgery.³ Other studies have shown that a lack of sleep is associated with increased pain and decreased pain tolerance/thresholds.⁴⁻⁷ For example, one study categorized participants in sleepy or non-sleepy groups based on their responses to a sleep questionnaire. Participants then

underwent pain sensitivity testing, and those who were in the sleepy group were unable to tolerate the same amount of pain as those who were in the non-sleepy group.⁵ Another study looked at patients who received a TKA who also had a sleep disorder (insomnia). Those with a sleep disorder had significant differences in VAS pain score, active ROM, and length of stay (LOS) in the hospital.⁸ Not only does a lack of sleep post-surgery impact pain, disturbed sleep can mediate the relationship between pain in the month post-surgery and functional limitations at 3 months post-surgery.⁹

Knowing the myriad of health benefits that sleep provides and sleep's association with pain post-operatively, it follows that promoting adequate sleep is an important tool, surgeons have to positively impact post-operative outcomes in their patients (e.g. decreased pain, better patient reported outcomes, and decreased use of opioids to manage pain). One pharmacological tool that physicians have used to increase sleep in patients post-operatively is zolpidem (Ambien). Although zolpidem is a non-benzodiazepine compound, it binds to GABA receptors at the same location as a benzodiazepine, increasing the activity of GABA and promoting sleep.¹⁰ Another non-pharmacological tool that physicians can use is cognitive behavioral therapy for insomnia (CBT-I). CBT-I has been proven to normalize sleep, improve sleep efficiency, and increase length of sleep in insomniacs.^{11,12} In fact, in a recommendation from the American College of Physicians, CBT-I is considered the first-line treatment for patients having trouble sleeping.¹³

Considering that both zolpidem and CBT-I are methods that can be used to increase sleep, and increased sleep is associated with decreased pain, a review of the literature was performed to determine if pharmacologic and/or non-pharmacologic sleep aids are shown to improve patient outcomes post-surgery. The purpose of the review was to determine if using the sleep aids were associated with decreased pain, decreased opioid use, and better outcomes.

Materials and Methods

A search of "sleep post-surgery" resulted in a total of 1981 articles from Medline and Pubmed, and 145,000 from Google Scholar. A search of "zolpidem post-surgery" resulted in 5 articles from Medline and Pubmed and 8,070 from Google Scholar. A search of "CBT and surgery" resulted in a total of 971 articles from Medline and Pubmed, and 35,400 from

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Key words: Sleep, post-operative pain, opioid use.

Contributions: KP, manuscript writing and references search; EM manuscript reviewing.

Conflict of interests: The authors declare no potential conflict of interests.

Funding: None.

Received for publication: 13 September 2019.
Accepted for publication: 27 October 2019.

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Orthopedic Reviews 2019; 11:8306
doi:10.4081/or.2019.8306

Google Scholar. A search of "zolpidem and pain" resulted in a total of 78 studies from Medline and Pubmed and 20,500 from Google Scholar. Studies were excluded based on criteria including: written in the English language, published in a journal, on human subjects, looked at post-surgical sleep, used zolpidem. After exclusion criteria were met, there were 11 studies left for review. Eight of the studies found were comparing zolpidem to a placebo or CBT to a placebo; only three studies compared both zolpidem and CBT.¹⁴⁻¹⁶ The outcomes of all the studies were measured as at least one of these six outcomes post-surgery: (1) amount of narcotics taken, (2) pain, (3) ROM, (4) quality of life, (5) satisfaction, and (6) subjective and objective measures of sleep.

Zolpidem/Ambien

Zolpidem (Ambien) is an oral sleep aid that falls into the medication class sedative-hypnotics.¹⁷ People who have trouble sleeping commonly take a 10 mg dose once per night for 7-10 days. Though zolpidem should not be taken long term because it can lead to addiction, it has been shown to induce sleep in the short term.¹⁷ Given that sleep is helpful in reducing pain and increasing pain tolerance, several studies have tried to determine if taking zolpidem after an orthopedic procedure will significantly reduce the patients' pain, reduce opi-

oid usage, and increased patient outcomes.

One study randomly assigned 29 patients who had undergone an ACL reconstruction to a zolpidem or placebo group for one-week post-surgery.¹⁸ The researchers found that those in the zolpidem group took 28% less narcotics than those in the placebo group. However, they did not find significant differences in post-operative pain levels between the two groups. Tashjian *et al.* randomly assigned 68 knee arthroscopy patients to three groups: zolpidem (24 patients), control (24 patients), or placebo (20 patients) to receive treatment for one-week post-op.¹⁹ They found that patients in the zolpidem group took less hydrocodone/ibuprofen and demonstrated improved daily post-op pain and fatigue. Those in the placebo group showed the same trends as those in the control group, but the trends were not significant. Cho *et al.* studied 78 patients randomly assigned to zolpidem or control groups for five days after rotator cuff repair.²⁰ The researchers found that those in the zolpidem groups used fewer pain medications, but VAS pain scores did not differ between the two groups. Further studies have tried to experimentally determine the effect of zolpidem on patients who have undergone a TKA. Gong *et al.* randomly assigned 148 patients to zolpidem and placebo groups for two weeks.²¹ They found that the patients in the zolpidem group had greater quality of life, better satisfaction, lower pain scores, and took less antiemetics. They also found a significant correlation between sleep quality and ROM. Wang and Zhou randomly assigned 180 TKA patients to zolpidem or placebo groups for six days and found that the zolpi-

dem group had better sleep quality, quality of life, VAS satisfaction, lower VAS pain scores, and less opioid use.²² Krenk *et al.* randomly assigned 20 patients with a TKA and THA to zolpidem or a placebo for one night post-surgery.²³ They used polysomnography (PSG) to objectively measure the participants sleep as well as subjective measures, and found that although the objective PSG did not show any significant objective differences in the sleep patients' were getting, patients' subjective reports from the zolpidem group had less fatigue, better sleep quality, and fewer arousals. Of the six total randomized control trials reviewed, five looked at post-operative opioid use as one of their outcome variables. All five studies found that those in the zolpidem groups had decreased opioid use.¹⁸⁻²² A review of pain management after outpatient ACL reconstruction confirmed this finding as well.²⁴ Another important outcome variable is pain reduction post-surgery. Of the studies reviewed, three found that the patients taking zolpidem had reduced pain,^{19,21,22} and 2 found no difference in pain levels in those who took zolpidem versus those who did not.^{18,20} However, it is worth noting that the studies that found significant differences in pain levels generally had larger sample sizes (e.g. 68, 148, and 180) than those studies that found no differences in pain levels (sample sizes of 29 and 78). Two studies also used quality of life as an outcome variable, and both studies found that patients taking zolpidem had increased quality of life.^{21,22}

A summary of studies using zolpidem is presented in Table 1.

Cognitive Behavioral Therapy for Insomnia (CBT-I)

CBT-I is a kind of psychotherapy aimed at changing thoughts and behaviors in order to encourage natural sleep. Although some CBT treatments are performed over an extended period of time, many current options are available through apps and audio tracks that patients can use on their smartphones when needed. Given the side effects and drug-drug interactions that can result from taking many medications, psychological interventions are a valid alternative in pain management and have been proven to reduce pain in chronic illnesses.^{25,26} For example, cognitive behavioral therapy (CBT) specifically has been shown to reduce pain severity in diabetic peripheral neuropathy,²⁷ and in a review of psychological treatments for post-surgical pain, Nicholls *et al.* found that CBT improves pain after surgery.²⁸ With regards to sleep, Omvik *et al.* compared the efficacy of CBT-I to zopiclone (a drug in the same class as zolpidem) and found that patients undergoing CBT-I had improved sleep efficiency and woke up less during the night compared to zopiclone and the placebo group.²⁹ In another study comparing CBT-I to zolpidem, Jacobs *et al.* randomly assigned patients with insomnia to CBT-I, zolpidem, or CBT-I+zolpidem groups.³⁰ The researchers found that the patients in the CBT-I group had decreased sleep onset latency, increased sleep efficiency, the most normal sleepers after treatment, and those patients maintained their improved sleep at long term follow-up. Moreover, other

Table 1. Summary of studies using zolpidem.

Authors	Year	Number of Patients	Surgery	Outcomes
Tompkins <i>et al.</i>	2011	29 randomized to zolpidem or placebo for 1 week	ACL reconstruction	Zolpidem group took 28% less narcotics. No significant differences in post-op pain levels.
Tashjian <i>et al.</i>	2006	68 total patients: 24 zolpidem, 24 controls (ibuprofen and hydrocodone), 20 placebo. Followed for 7 nights post-op	Knee arthroscopy	Control and placebo group had worse mean daily post-op pain and fatigue. Control group took more hydrocodone and ibuprofen than patients in zolpidem group.
Gong <i>et al.</i>	2015	148 total patients: 74 zolpidem, 74 placebo for two weeks	Total knee arthroplasty (TKA)	Zolpidem had greater quality of life and satisfaction, lower pain scores, and took fewer antiemetics. Significant correlation between sleep quality and ROM.
Cho <i>et al.</i>	2015	78 total patients: 39 multi-modal analgesia and zolpidem, 39 only multimodal analgesia. 5 days post-op.	Arthroscopic rotator cuff repair	Followed the number of days patients needed a rescue analgesic (2.1 +/- 2.0 with zolpidem and 3.3 +/- 2.8 in control). VAS pain scores no different.
Krenk <i>et al.</i>	2014	20 total patients: 10 zolpidem, 10 placebo 1 night post-surgery.	Total hip and knee arthroplasties	Polysomnography showed no significant differences in sleep Zolpidem group had less fatigue, better sleep quality, and fewer nighttime arousals.
Wang <i>et al.</i>	2017	180 total patients randomized to zolpidem or placebo group	Total knee arthroplasty	Zolpidem group had better sleep quality, quality of life, VAS pain score, and less opioid use.

Table 2. Summary of studies using CBT.

Authors	Year	Number of patients	Surgery/Pathology	Outcomes
Otis <i>et al.</i>	2013	20 participants: 12 CBT, 8 in treatment as usual.	Diabetic peripheral neuropathy	CBT group had decreased pain severity.
Omvik <i>et al.</i>	2006	46 patients randomized to CBT (18), zopiclone (16) or placebo (12) for 6 weeks.	Insomnia	CBT group had improved sleep efficiency, less time in slow wave sleep (stages 3 and 4), and woke up less during the night.
Kwekkeboom <i>et al.</i>	2010	30 patients	Cancer	Significant decreases in pain, fatigue, and sleep disturbances immediately after the use of the CBT. No difference after 2 weeks.
Jacobs <i>et al.</i>	2004	63 randomized to CBT, zolpidem, or CBT+zolpidem groups	Insomnia	CBT improved sleep efficiency and yielded more normal sleepers after treatment. Combined treatment was not better than CBT alone.

researchers have found that using CBT as an intervention in patients with cancer has resulted in decreases in pain, fatigue, and sleep disturbances.³¹ Patients with pain and illness tend to have more trouble sleeping and treating the insomnia with CBT-I seems to improve sleep as well as pain.¹⁶ A summary of studies using CBT is presented in Table 2.

Discussion and Conclusions

Orthopedic surgeons are the third highest prescriber of opioids in the US.³² With the alarming nature of the opioid epidemic right now, it is integral for orthopedic surgeons to find alternate ways to help their patients manage their pain. It is clear that sleep (and lack thereof) plays a role in patients' perception, tolerance, and ability to deal with their pain, so one route available to an orthopedic surgeon to decrease opioid use is to encourage better sleep in their patients, especially post-surgery.

One pharmacological method to increase sleep is zolpidem. Zolpidem is a well-documented sleep aid that was shown to decrease opioid consumption, reduce pain, and increase quality of life when used for a short period of time following orthopedic procedures. However, the type of sleep that zolpidem induces is much different than our natural sleep, and as a result does not confer the same health benefits.¹ In fact, use, and especially abuse, of zolpidem and other sleeping pills can damage patients' health and be a risk factor for life-threatening diseases.¹

Because of the risks associated with zolpidem and pharmacologic sleep aids, it is important for physicians to look at non-pharmacologic means of helping their patients sleep, such as CBT-I. CBT-I has been shown to be effective in increasing the quality of sleep and sleep time, decreasing sleep onset latency, decreasing pain, and

helping patients keep those gains over longer periods of time. CBT-I is a valid non-pharmacologic alternative to zolpidem when thinking about how to improve sleep, and ultimately post-operative pain in patients.

Futures directions

It is clear that CBT-I is a valid tool to help patients sleep and deal with pain. However, no study has specifically looked at CBT-I and sleep in an orthopedic surgical setting. Future randomized control trials looking at CBT-I, sleep, and how those two variables are related to post-operative pain and opioid use could be beneficial to the field of orthopedic surgery as we try to find ways of helping patients deal with pain without the use of narcotics. Further studies would also be beneficial to learn more about why patients taking zolpidem have better outcomes when we know that the sleep they are getting from taking a sleep aid is not the same as natural sleep. Is it that some sleep, even unnatural sleep, is better than no sleep at all? Or is the sleep from zolpidem conferring some but not all of the health benefits? As we continue to address the current opioid epidemic, it is important to continue to explore other methods for post-operative pain management.

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