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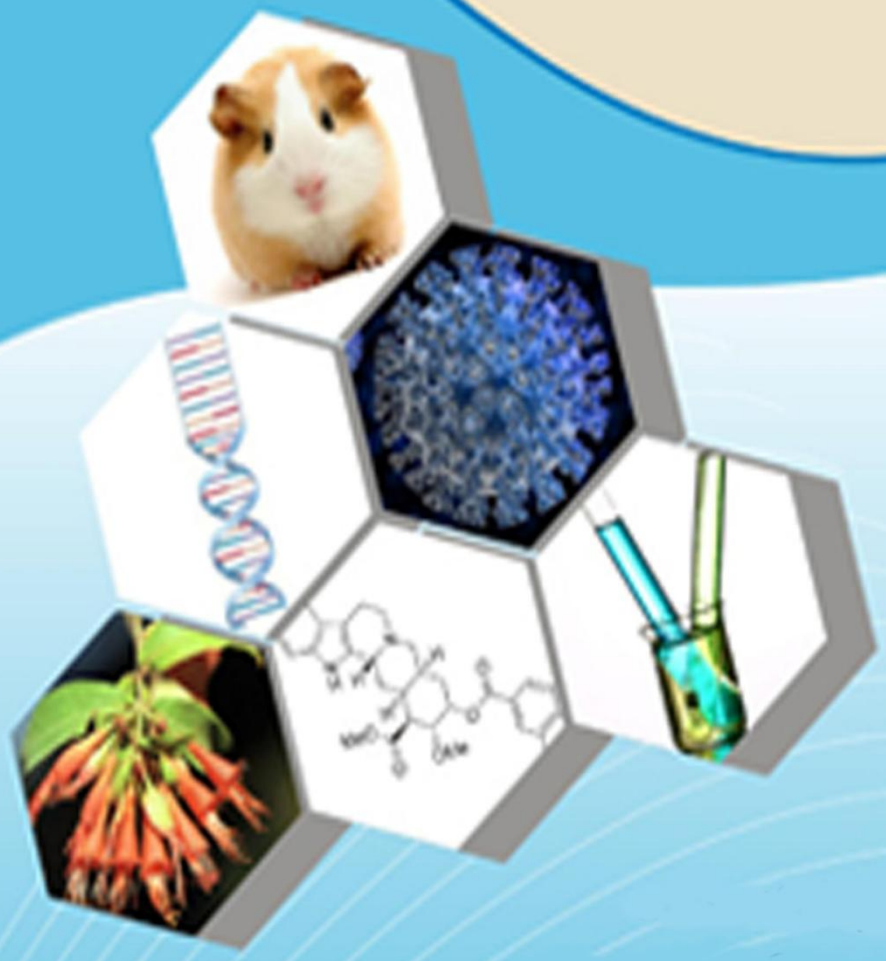

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Pharmacological Treatment of Postoperative Sleep Disorders in the First Two Nights. Examination in Detail

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Abstract

The restorative benefits of sleep are especially important to take into account in the immediate postoperative period. Acute sleep disturbances after surgery are seldom discussed in the medical literature. Most pharmaceutical treatments include the use of benzodiazepines, however because of their potential for adverse effects, it is highly advised that a tailored approach be used. The purpose of this narrative review was to analyze effective pharmacological treatments for acute sleep problems in the first 48 hours after surgery in patients who had planned medical operations. A narrative search was performed in the databases of Embase, PubMed, and Cochrane. No studies other than randomized controlled trials and systematic reviews were examined.

The effectiveness of pharmaceutical therapies for acute sleep problems, the methods of administration, and the effect on postoperative descents were the major outcomes. The original search turned up 271 papers, however only 7 were suitable for inclusion. Pharmacological treatments like 5mg of Zolpidem before bed and >900mg of Gabapentin are often used. The first postoperative phase is crucial for treating these diseases, and it has been found that Dexmedetomidine IV infusion at a dosage of 0.05 mcg/kg/h is effective.

Keywords: AcutePain;PostoperativePeriod;SleepDisorders;HypnoticsandSedatives;Adrenergicα-Agonists

1. Introduction

Age, surgery, anesthetics, postoperative anxiety, and other physical and mental stresses [1-3] (Table 1) all increase the risk of developing a sleep problem in the postoperative period. In most cases, the symptoms of these diseases only endure for a few days and go away completely after the underlying cause of stress has been removed or the individual has learned to cope with it.

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Table1: DrugInducedsleepdisorders

Drug	Type	Mechanismaction	Indication
Metoprolol, Labetalol	B blockers	Suppressendogenousnighttimemelatonin secretion.	Heartfailure,hypertension,myocardialinfarction, atrial fibrillation, migraine prophylaxis,intra-cerebralhemorrhage
Clonidine	α-2adrenoceptoragonist	Alterthe NREM/REM sleep cyclebyreducingREMsleep	Hypertension,pain
Methyldopa	Central sympathetic agent, false neurotransmitter	Stimulationofcentralinhibitoryαadrenergic receptors	Hypertension
Losartan	AngiotensinIIreceptorantagonist	BlockingangiotensinIIcanraisepotassiumlevelsbyblocking aldosteronesecretion	Hypertension,nephropathyintype2diabetes
Atorvastatin, Simvastatin, Rosuvastatin	Statin	Inhibitionofthesynthesis of isoprene,aproductformedinthebiosynthesisofcholesterol	Hypercholestelomia
Sertraline, duloxetine, IMAO	Antidepressants(SSRIs)	Activation of serotonergic 5-HT2receptorsandincreasednoradrenergicanddopaminergic neurotransmission	Majordepressivedisorder,generalizedanxiety disorder, neuropathic pain, muscleskeletalpain
Prednisone	Corticosteroids	Elevatedafternoonplasmacortisollevelshavebeenassociatedwithinsomnia.	Allergic conditions, dermatologic diseases,endocrine conditions, hematologic diseases,neoplasticconditions,rheumatologic conditions,pulmonarydiseases.

A therapeutic intervention is necessary in certain circumstances [4-6] because sleep disturbances, despite their brief duration, are a severe worry for both patients and their loved ones and hinder patients' recovery. It is possible that poor sleep habits formed in the postoperative period contribute to the development of chronic sleep disorder in patients who suffer these problems for more than a few days. Indeed, mental and physical health, and the optimal physiological and emotional functioning that results, are inextricably linked to one's sleep habits and sleep cycle. Regarding memory, mood, metabolic function, and inflammatory response, some research suggests a link between sleep disruptions and these illnesses [7].

Reduced total sleep time and slow-wave sleep, reduced REM (Rapid Eye Movement) sleep, and an increased length of the second stage of non-REM sleep are all sleep-related abnormalities that occur in the early postoperative period [8]. It has also been reported that in the first few days after surgery, patients typically report suffering sleep disruptions and sleep deprivation [9].

Surgical stress, environmental factors, medical treatments [9-14], and comorbidities like obesity, hypertension, diabetes, cardiovascular disease, and postoperative pain, the latter being a major risk factor for sleep disorders that acts in a bidirectional way since the pain experienced after surgery can make it difficult to fall asleep or stay asleep. Therefore, a cautious approach is required for the proper management of these disorders in the early postoperative period, as is taking into account the efficacy of the available treatments and their potential side effects, as sometimes drugs may be effective, but they can cause sedation, putting patients at risk for respiratory distress, aspiration pneumonitis, confusion, falls, and delirium [7]. The short-term treatment of sleep disorders with Z-drugs, non-benzodiazepines hypnotic agents (Zolpidem, Zopiclone, Eszopiclone, Zaleplon), and

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benzodiazepines has been reported to be effective in non-surgical patients [17]. Trazadone, diphenhydramine, and gabapentinoids have also been used off-label with some success in the management of sleep disorders.

As a result of the above, this literature review aims to describe in detail the various pharmacological alternatives available for the pharmacological therapy of acute sleep disturbances occurring within 48 hours following surgery in hospitalized patients. It is important to note that in the current study, acute sleep disorders are defined as conditions in which pharmacological management is warranted because patients in the postoperative period experience difficulties initiating or maintaining sleep, insufficient sleep duration and quality, and early morning awakening.

2. Methods

A story is being reviewed here. PubMed, EMBASE, and COCHRANE were searched for relevant articles using the following keyword combinations: Disorders of sleep [insomnia OR sleep disruption OR sleep start] ...AND ['maintenance disorders' OR'sleep deprivation' OR'sleep anxiety'] OR [zolpidem OR eszopiclone OR zopiclone OR trazodone OR hydroxyzine OR diphenhydramine OR antihistamine OR amitriptyline OR lorazepam OR triazolam OR doxepin OR mirtazapine OR suvorexant ORmedications like "ramelteon" or "melatonin" or "clozapine" or "alprazolam" or "gabapentin" or "pregabalin"the antidepressants [escitalopram OR venlafaxine OR duloxetine] AND [postoperative OR postoperative time OR postoperative–post-anesthesia‖OR–post-anesthesiacare‖OR–postanesthetic‖OR–post-surgery‖OR–postoperativecare‖ OR–postoperativepain‖OR–postoperativesleep‖]AND[–inpatient‖or–hospitalpatient‖].Then,am anual search wascarriedoutin grayliterature sources(figure1).

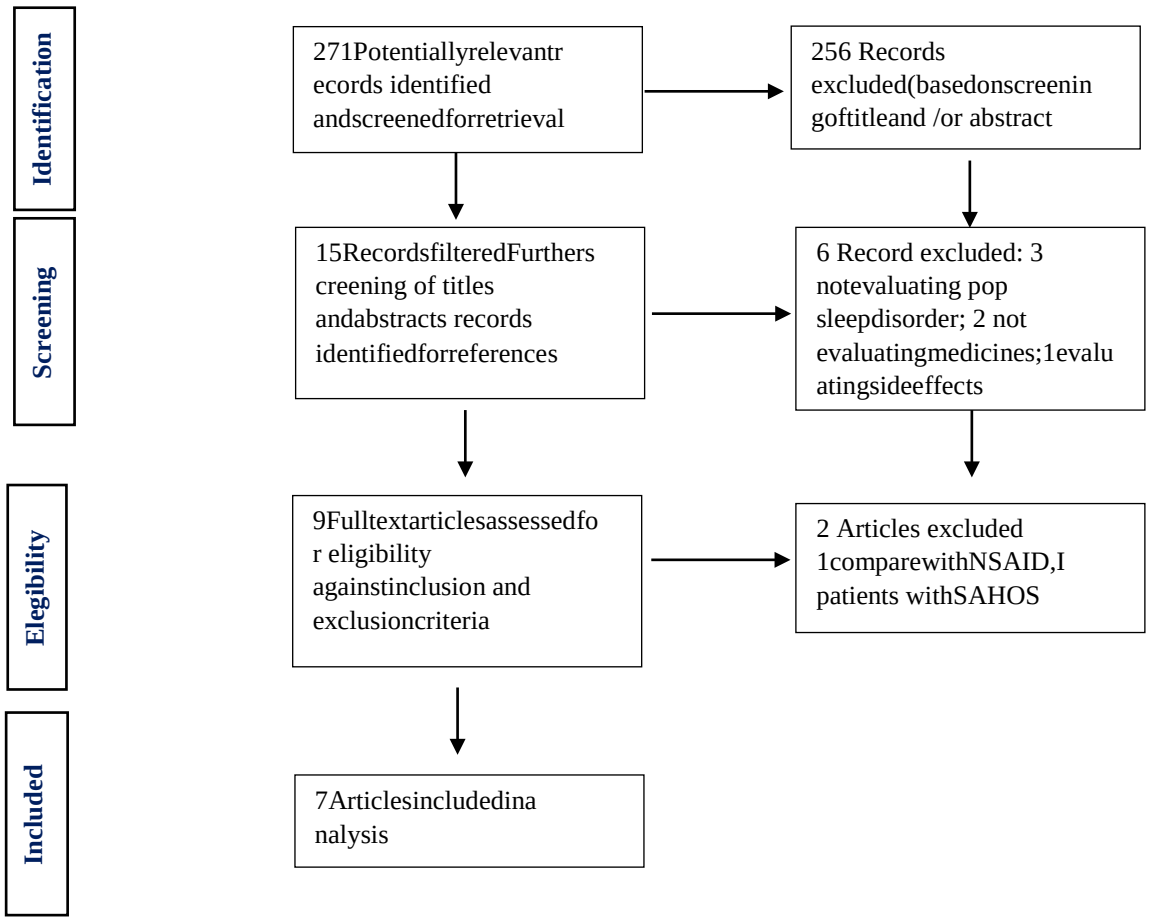

Figure1: Flowchartofarticle search

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2.1 InclusionCriteria

Randomized and controlled clinical trials conducted in postoperative care patients who underwent electivesurgery and who were older than 18 years and had a postoperative follow-up ≥ 48 hour. Only studies publishedinEnglishorSpanishand between2010and 2019wereconsideredforinclusion.

2.3 Exclusioncriteria

Thefollowingstudies wereexcluded:
Studiesonothertypesofsleepdisorderslikehypersomnia,obstructivesleepapnea,chronicinsomnia.
Studiesconductedinpatientswithahistoryofpharmacologicalmanagementforinsomniaorinpatientswithsleep disorderscausedbyotherconditionsthanbeinginapostoperative period.
Case-series.
Studiesconductedinpediatricorobstetricpatients.
Casereports. (Table2)

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3. Results

Theinitialsearchyielded271studies.However,oncetheywerefullyreviewed;7articlesmettheinclusioncriteriaandwereincluded foranalysis(Table 2)[9,19–22,24,25].

Table2: Maincharacteristicsofthestudiesincludedinthereview.

Study	Population	Intervention	Comparison	Methodology/Instrument
Eloyetal.[19]	29patientswhounderwentorthopedicsurgeryofthelowerlimb	Administration of 400mg/day of Gabapentinonthedayofsurgery onedayaftersurgery	Placebo	PSQI(7 categoriesof0-3)
Lunnetal.[20]	300patientswhounderwenttotalkneereplacement	Gabapentin was administered to 2 outof3groupsindifferentdoses: -GroupA:1300mg/day -GroupB:900mg/day - GroupC:placebowasadministered for 6daysaftersurgery	Placebo	Sleep quality was measuredaccordingtoasubjectivenumericalscale(0=nosleepproblemsatalland10 =theworstexperienceregarding sleep)
Spenceetal.[21]	70patientswhounderwent shoulder arthroscopy	Gabapentin was usedevery 12 hours for 2daysaftersurgeryatdosesbetween300 and600mg/day	Placebo	Sleep quality was measuredusing a Likert scale (over 5points). Total sleep durationwasalsomeasured(in hours)
Gongetal.[22]	148patientswhounderwenttotalkneereplacement	A 5mg/day Zolpidemvsplacebowasadministeredfor14 days	Placebo	Sleepefficiencywasassessed during14daysaftersurgeryby meansof polysomnographicstudies

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Chenetal. [9]	59patientswhounderwent abdominalhysterectomy	AdministrationofDexmedetomidine+SulfentanilIV 0.05 mcg/kg/h Dexmedetomidineinfusion	Sulfentanil IV	Sleepefficiencywasmeasured using polysomnography the first 2nightsaftersurgery
Buvanendranet al.[24]	240 patients who underwent total kneereplacement	300mgofPregabalin was administeredbeforethesurgery	Placebo	Sleep problems were measuredaccordingtoanumericalscale(0=nosleeping problems and 10 =facingtheworstsleep problems)
Andersenetal.[25]	44aged18-70whounderwentlaparoscopiccholecystectomy	A10mgmelatoninIVdosewas administered toinducesleep30minafter surgery	Placebo	Sleep quality was measuredusingthe Karolinska scale (KSS, 1 =extremelyalert,9=extremelyasleep)fromday 1 to day 3 of the postoperativeperiod.

Source:Ownelaboration.

3.1 Zolpidem

Zolpidem, like benzodiazepines, is a GABAA receptor chloride channel agonist that enhances GABA inhibitory effects and causes sleepiness. Improvements in sleep quality were associated with less knee pain in the early postoperative period for patients taking Zolpidem, according to a study by Gong (2015) [22] on the effects of sleep quality on early recovery after total knee arthroplasty (n=148). Sublingual pills, an oral spray, regular tablets, and extended-release tablets are all ways to take this medication. Headache, dizziness, sleepiness, nausea, diarrhea, myalgias, rebound insomnia, memory and behavior difficulties have all been linked to the usage of Zolpidem in adults. Zolpidem has been shown to be equally effective as benzodiazepines in treating insomnia while causing less negative side effects [28]. Another randomized, double-blind research comparing Zolpidem to a placebo in 20 patients (60 years) undergoing hip and knee replacements under spinal anesthesia found no significant difference between groups after surgery. This study was conducted by Krenk et al. (2014) [29]. Consequently, our data suggests that giving patients 5mg of Zolpidem on the first night after surgery to treat their sleep disturbances is beneficial. The current labeling for Zolpidem recommends a starting dosage of 5 mg taken before bedtime for the short-term treatment of insomnia due to difficulty initiating sleep.

3.2 Gabapentin

Gabapentin is an alkylated derivative of the neurotransmitter gamma-aminobutyric acid (GABA) that is used to treat partial-onset seizures and postherpetic neuralgia in adults. Binding to the 2-1 subunit of voltage-gated Ca2+ channels causes a decrease in the influx of Ca2+ and the release of excitatory neurotransmitters like glutamate at the synapse, thereby decreasing the hyperexcitability of the nociceptive neurons and their ability to transmit pain and cause central sensitization. When given before to surgery, Gabapentin lessens the need for opioids and their negative side effects, as well as the severity of postoperative pain. Sedation and dizziness are the most common adverse reactions, however peripheral edema has also been seen [30,31]. In a study of patients who had undergone a complete knee replacement, Gabapentin was shown to increase slow-sleep waves, decrease early waking events, and preserve REM sleep compared to a placebo group [32,33].

While Lo et al. [34] noted that the risk of sedation and visual disturbances increased with increasing doses of Gabapentin, it was reported that the drug improved patients' sleep quality during the first two nights following surgery.

In contrast to these results, Eloy et al. [19] found that Gabapentin does not reduce postoperative pain or improve sleep quality when tested in a study of patients who had undergone total hip or knee replacement using the Pittsburg Sleep Quality Index (PSQI). Similarly, Spence et al. [21] found that Gabapentin did not enhance the length or quality of sleep in individuals undergoing shoulder arthroscopy compared to a placebo. Polysomnographic studies have been conducted to examine the impact of gabapentin on sleep disturbances. For instance, one research indicated that a dosage of 600 mg/day was most effective in treating insomnia in a group of 18 individuals [18], while another reported that a dose of up to 900 mg/day was necessary (540 mg/day average dose) [35]. Dosages stated there may differ from those found in the research since Gabapentin was titrated for up to 3 weeks to find the optimal dosage.

Since there is not enough information to identify the proper amount and the kind of surgical operation it may be used for, the results given above suggest that regular use of Gabapentin

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for the treatment of sleep disturbances during the postoperative period should not be suggested.

3.3 Pregabalin

Indicated for the management of severe diabetic peripheral neuropathy, postherpetic neuralgia, partial-onset seizures, fibromyalgia, and neuropathic pain associated with spinal cord injury, Pregabalin, like Gabapentin, operates via voltage-dependent calcium channels [30]. Pregabalin's effectiveness in treating sleep problems is little understood. Polysomnographic studies, however, have shown that it affects sleep-maintenance insomnia and is helpful in the management of sleep disorders due to a wide variety of conditions, such as fibromyalgia, GAD, neuropathic pain, and postherpetic neuralgia [36,37].

Pregabalin was shown to be useful in reducing the frequency of sleep disruptions on the first postoperative night, according to a randomized, placebo-controlled, double-blind experiment conducted by Buvanendran et al. [24]. Patients using pregabalin experienced significantly (P 0.0001) less disruption to their sleep than those taking a placebo.

3.4 Melatonin

Pineal glands produce melatonin, an endogenous hormone. There is evidence that melatonin plays a function in sleep regulation due to the association between its elevated nocturnal production and its higher levels at the start of nights [38,39]. The FDA does not oversee the use of melatonin as a treatment for sleep problems since it is considered an alternative medicine.

Melatonin has been indicated for the therapy of acute sleep disturbances [39], and it has been documented in patients with sleep abnormalities related to their circadian rhythm and in geriatric people. The effects of melatonin on postoperative sleep and pain in patients who had undergone total knee arthroplasty were studied in a randomized, double-blind pilot research by Kirksey et al. [40].

When compared to the placebo group, those who were given melatonin did not sleep any more effectively ($p = 0.15$) or for any longer ($p=0.067$) [36].

A randomized, placebo-controlled, double-blind trial conducted by Andersen et al. [25] on 44 patients who had cholecystectomy found that a melatonin dosage of 10mg had no impact on sleep quality in the first three days after surgery. Although headache and dizziness are the most often reported adverse effects of this medication, some users have also seen an improvement in their ability to fall asleep faster. Patients who had laparoscopic cholecystectomy and were given melatonin at 5mg/day did not demonstrate any increase in sleep quality compared to those who were given placebos, as stated by Gögenur et al. [41]. These results suggest that melatonin is not useful for treating sleep disturbances in those receiving postoperative treatment.

Dexmedetomidine, 3.5mg/kg

Dexmedetomidine is a highly selective agonist of alpha-2 adrenergic receptors with sedative, analgesic, and anxiolytic effects that does not affect respiratory rate. It binds to alpha-2 receptors with a 1610-fold higher affinity than alpha-1 receptors [42]. The adrenergic inputs that promote awakening in the cortex, basal forebrain, thalamus, and hypothalamus are reduced when it binds to -2 adrenergic receptors in the locus coeruleus, thereby exerting a function in the initiation and maintenance of sleep. In addition, they produce sleep via regulating non-adrenergic neurons in the thalamus and the frontal lobes [43]. Dexmedetomidine induces a condition similar to N2 sleep by acting on an endogenous sleep-promoting route, making it unique among sedatives. Dexmedetomidine aids in maintaining sleep cycles and improving sleep efficiency in critical care unit patients who are ventilator-dependent. It has also been shown that infusion of this medicine enhances total sleep time [44] in elderly patients under postoperative care who are not on ventilators. Dexmedetomidine promotes N3 stage sleep in a dose-dependent manner without affecting the psychomotor vigilance test scores, according to a prospective, randomized, and crossover pilot study by Akeju et al. [43] in 10 patients comparing the effects of dexmedetomidine and zolpidem for sleep induction.
Researchers Chen et al. [45] studied the effects of postoperative dexmedetomidine infusion on sleep quality in 60 patients undergoing abdominal hysterectomy. They discovered that giving patients undergoing abdominal hysterectomy a combination of dexmedetomidine infusion and sufentanil resulted in significantly better sleep efficiency and fewer early waking episodes than giving patients sufentanil alone. These patients also had improved pain management. Patients who had partial laryngectomy and were given Dexmedetomidine and sufentanil slept better in the postoperative period than those who were given sufentanil alone, according to a research by Qin et al. [36].

4 - Discourse

The effectiveness of pharmaceutical therapy of acute sleep disturbances in patients requiring postoperative care is little documented. The findings of the research by Eloy et al. show that gabapentin does not help patients with sleep following

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orthopedic surgery. Better sleep quality for the first two nights following surgery was a secondary result in the trial by Lunn et al., which compared groups treated with gabapentin and placebo. Both groups (300 mg gabapentin or placebo 1 hour before surgery) in a 2011 trial on shoulder surgery conducted by Spence et al. slept similarly [21]. Gong L, et al., discovered in their research [22] revealedzolpidem-treated patients showed more improvement in quality of life, and that there was a discernible link between sleep quality and mobility. These findings indicated that higher quality sleep aids patients in their recovery after a total knee or hip replacement. Chen et al. [9] found that giving patients dexmedetomidine after surgery considerably enhanced the quality of their sleep. Patients using pregabalin slept better than those taking a placebo while hospitalized, according to a research by Buvanendran et al. [24]. Anderson et al. [25] observed no statistically significant changes in sleep quality between the placebo and intravenous melatonin groups. Because of this, non-pharmacological measures like earplugs and masks [46] and complementary measures commonly known as sleep hygiene should be considered as the first options for the management of these disorders; however, they are time-consuming, and sometimes the rapid discharge of these patients does not allow for their implementation. Acute sleep problems may be induced by the stress experienced by patients in the days leading up to surgery, thus it is not uncommon for adult patients without a history of sleep disorder to report having poor sleep patterns following surgery. These diseases tend to be short-lived and fade away after the triggering event has passed. With this in mind, the objective of pharmacologic treatments in postoperative care is to lessen the emotional and physiological strain that patients experience as a result of sleep deprivation. In addition, treating short-term sleep issues might lessen the likelihood of long-term sleep problems from stemming from abnormal cognitive and behavioral reactions to sleep loss. For the treatment of severe sleep disturbances interfering with these patients' daily lives and recovery, hypnotic medication therapy should be explored following the adoption of non-pharmacological therapies; nevertheless, hypnotics should only be recommended for brief periods of time. Benzodiazepines including the Z-drugs zaleplon, zolpidem, and zopiclone are some of the hypnotics that have been licensed for the treatment of insomnia.

4. Conclusions

Patients in intensive care units or with postoperative delirium are good candidates for the management of sleep disorders through the intravenous administration of Dexmedetomidine. Gabapentin at doses greater than 900 mg/day and Zolpidem at a dose of 5 mg at night may have a positive impact on sleep efficacy in the early postoperative period. However, hypnotics have undesirable side effects, thus non-pharmacological approaches are strongly encouraged. Sleep quality in postoperative care patients has not been well studied to develop a standard of measurement or to identify the most effective pharmacological therapy.

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