Purpose of review
We reviewed evidences regarding occurrence, risk factors, harmful effects, prevention, and management of sleep disturbances in patients after surgery.

Recent findings
Normal sleep is important to maintain physical and mental health. Sleep disturbances frequently occur in patients after surgery. Factors associated with the development of postoperative sleep disturbances include old age, preoperative comorbidity, type of anesthesia, severity of surgical trauma, postoperative pain, environment stress, as well as other factors leading to discomfort of patients. Development of sleep disturbances produces harmful effects on postoperative patients, that is, leading to higher risk of delirium, increased sensitivity to pain, more cardiovascular events, and poorer recovery. Both nonpharmacological and pharmacological measures (such as zolpidem, melatonin, and dexmedetomidine) can be used to improve postoperative sleep. Recent evidences show that sleep promotion may improve patients’ outcome, but requires further evidences.

Summary
Sleep disturbances are common in patients after surgery and produce harmful effects on postoperative recovery. Sleep-promotion therapy may be helpful to improve postoperative recovery, but long-term effects deserve further study.

Keywords
outcomes, postoperative complications, sleep disturbances, sleep promotion

INTRODUCTION
Sleep disturbances frequently occur in patients after surgery, and its occurrence is harmful for postoperative recovery [1–5]. Recent evidences show that multiple perioperative factors are related to the development of postoperative sleep disturbances; some of these factors can be properly managed to reduce the severity of sleep disturbances, and sleep promotion may improve postoperative recovery. Here we reviewed evidences regarding occurrence, risk factors, harmful effects, prevention, and management of sleep disturbances in patients after surgery.

NORMAL SLEEP AND SLEEP STRUCTURE
Sleep is a naturally recurring state of mind and body, which is characterized by lowered consciousness, relatively inhibited sensory activity, inhibition of nearly all voluntary muscles, and reduced interactions with surroundings. According to the polysomnographic study results, sleep is divided into nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep can be further divided into stage 1 (N1, also called light sleep, accounting for 5–10% of total sleep in adults), stage 2 (N2, accounting for 45–55% of total sleep in adults), and stage 3 (N3, also called deep sleep or slow wave sleep (SWS), accounting for 15–25% of total sleep in adults). REM sleep accounts for 20–25% of total sleep in adults.

Normal sleep has a significant circadian rhythm and cycles in the order of N1 → N2 → N3 → N2 → REM. In healthy adults, the duration of each cycle lasts approximately 90 min. N3 sleep or SWS is a deep stage and is considered the most restful form of sleep. The sleeper is less responsive to the environment and restores the body. Night terrors, nocturnal enuresis, sleepwalking, and somniloquy...
often occur in this stage. During the stage of REM sleep, high-frequency electroencephalographic waves that are similar to a waking state appear, but sleeper is harder to arouse than other stages. Vivid dreams may occur during this stage [6]. Lack of REM sleep impairs the ability to learn complex tasks, and deprivation of REM sleep often results in rebound in REM sleep, that is, more REM sleep than usual.

Sleep structure changes across the aging process. Compared with the young, sleep in the elderly tends to show short duration, frequent wake, decreased N3 sleep, and early wake [7]. For healthy older adults of 75 years, normal sleep usually requires a total sleep time of about 6 h; of which, 11, 57, 12, and 20% are the stage N1, N2, N3, and REM sleep, respectively.

SLEEP DISTURBANCES AFTER SURGERY
Patients often develop significant sleep disturbances immediately after surgery, especially major surgery. Polysomnographic manifestations usually include severe sleep deprivation, sleep fragmentation, and decrease or loss of SWS and REM sleep during the night after surgery [1,2,6–9]. Patients may report decreased sleep time, increased numbers of arousals or awakening, lowered sleep quality, and frequent nightmares [10]. During the subsequent postoperative period, sleep structure gradually returns to normal with a REM rebound within 1 week [2].

FACTORS ASSOCIATED WITH POSTOPERATIVE SLEEP DISTURBANCE

Age
Aging is associated with sleep structure changes; furthermore, elderly are more difficult to adjust their sleep to environmental changes [10,11]. In the study of Chung et al. [9], higher age is associated with higher apnea–hypopnea index (AHI) and lower sleep efficiency after surgery. Therefore, elderly patients are more prone to develop postoperative sleep disturbances.

Preoperative comorbidity
Patients with preoperative obstructive sleep apnea (OSA) are at increased risk of postoperative sleep disturbances. Studies found that patients with a higher preoperative AHI are predicted to have a higher AHI after surgery [8,9]. Severe preoperative coronary artery disease is also associated with worse sleep quality after surgery. In a small sample size study of Yilmaz et al. [12], 52 patients undergoing coronary artery bypass graft surgery were assessed for postoperative sleep quality with Pittsburgh Sleep Quality Index. The results showed that patients with preoperative myocardial infarction had significantly worse sleep quality after surgery, and higher preoperative angina score was an independent predictor of poor sleep quality after surgery. However, effects of other preoperative comorbidity on postoperative sleep quality remain unclear.

Type of anesthesia
Regional anesthesia is helpful to relieve sleep disturbances after surgery. In a randomized controlled trial, 162 women scheduled to undergo fast-track abdominal hysterectomy randomly received either general or spinal anesthesia; the results showed that patients in the spinal anesthesia group experienced less bad sleep in the night after surgery [4]. In a cohort study of 376 surgical patients, regional anesthesia (when compared with general anesthesia) was associated with lower postoperative central apnea index [9]. One possible reason is that regional anesthesia reduced perioperative opioid consumption [4,9]. The impact of opioids on the development of postoperative sleep disturbances is also reported in other studies [2]. However, even when opioids are avoided and pain is well controlled, sleep disturbances still develop after surgery [13,14], indicating the effects of other factors.

Severity of surgical trauma
Sleep disturbances are more severe after major surgery. For example, in patients after open cholecystectomy under general anesthesia, significant sleep disturbances (manifested as increased N2 sleep, and decreased or lost N3 and REM sleep) occurred during the night of surgery [2]; whereas in patients after laparoscopic cholecystectomy under general anesthesia,
anesthesia, sleep disturbances were less severe (manifested as decreased N3 sleep but not REM sleep) during the same night [15]. Chung et al. [9] also reported similar results, that is, major surgery (when compared with minor surgery) is associated with lower sleep efficiency after surgery. However, minor surgery such as lumpectomy for breast cancer also produces sleep disturbance in the night after surgery, although less severe, which normalizes after 2 weeks [16].

Postoperative factors
Many postoperative factors are associated with the development of sleep disturbances. Among them pain is possibly the most important one [17*,18]. However, it is worth to note that opioid analgesia do not improve, but rather worsen postoperative sleep by decreasing REM sleep and increasing AHI [2,9]. Environmental factors including noise and lights in the ward, disturbances from healthcare staff, and disturbances from other patients are also important sleep disturbers [17*,18]. In the ICU, the noise levels can reach up to 85 dB with alarms and staff conversations [19]. In a general ward, the noise levels can be also as high as 70 dB [20]. Furthermore, various kinds of discomforts, such as needing to use toilet facilities, nausea, anxiety, fever, and others, lead to sleep disturbances as well [17*].

HARMFUL EFFECTS OF SLEEP DISTURBANCES ON POSTOPERATIVE OUTCOMES

Sleep disturbances and delirium
Sleep disturbances are considered important risk factors of delirium development. In patients undergoing arthroplasty or noncardiac surgery, preoperative sleep disruption was associated with an increased risk of postoperative delirium [21,22*]. In elderly patients undergoing arthroplasty, pre-existing OSA was a significant predictor of postoperative delirium [23]. In veteran patients enrolled in hospice, poor sleep quality was also associated with a high risk of developing delirium [24].

Sleep disturbances and pain
The relationship between sleep and pain is reciprocal; poor sleep also leads to increased sensitivity to pain. Studies of patients hospitalized for burn injury showed that significant temporal relationships exist between sleep, pain, and analgesic medication, that is, a night of poor sleep was followed by a significantly more painful day and higher analgesic intake; furthermore, high levels of pain and analgesic medication during the day were both significant predictors of poor sleep on the following night [25,26]. This is also true for patients with chronic pain [27].

Sleep disturbances and cardiovascular events
Sleep disturbances are associated with increased risk of cardiovascular events in high-risk patients. In a cross-sectional prospective cohort study, 388 patients after percutaneous coronary intervention were assessed for symptoms of disturbed sleep at 1 month and followed-up for at least 4 years for major cardiac events. The results showed a positive relationship between the number of sleep disturbance symptoms and the occurrence of major cardiac events (including cardiogenic death, myocardial infarction, and repeated revascularization). Each additional sleep symptom was associated with a hazard ratio of 1.2 ($P=0.001$) [5]. As showed in a systematic review, OSA in nonsurgical patients is associated with increased risk of stroke [28].

Sleep disturbances and postoperative recovery
Sleep disturbances have significant impacts on the recovery after surgery. In patients after fast-track hysterectomy, poor sleep quality during the first postoperative night was strongly associated with a longer hospital stay [4]. In patients after total knee replacement surgery, sleep disruptions 1 month following surgery was associated with functional limitations 3 months following surgery, indicating the importance of adequate sleep during postsurgical recovery [29]. In patients after kidney transplantation, sleep disorders were common (occurred in 30–62% of patients) and were associated with poorer emotional state and lower quality of life [30–32].

MEASURES TO IMPROVE POSTOPERATIVE SLEEP

Nonpharmacological measures
These include using regional anesthesia whenever possible [4,9], decrease the severity of surgical trauma (perform laparoscopic rather than open-abdominal surgery) [9,15], provide multimodal analgesia (to decrease opioid consumption) [2,17*,18], and remove ambient stressors during night [17*]. For patients admitted to the ICU after surgery, managements according to sleep care guidelines, such as maintaining a quiet and dim
environment and decreasing interruptions from care activities at night, improve sleep quality and sleep efficiency [33,34]. A meta-analysis showed that the use of ear plugs and eye mask is also helpful in promoting sleep among patients in ICU [35].

Pharmacological measures

A recent systematic review concluded that there is insufficient evidence to suggest that pharmacotherapy improves the quality or quantity of sleep in hospitalized patients [36]. The following drugs, however, are recently being used to improve sleep in postoperative patients.

Zolpidem

Zolpidem is a short-acting nonbenzodiazepine compound of the imidazopyridine class that increases the activity of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, by binding to GABA$_A$ receptors at the same location as benzodiazepines [37]. In a small sample size study of patients undergoing hip or knee replacement, zolpidem administered one night before and on the first night after surgery improved the feelings of sleep quality and fatigue but not sleep architecture [38].

Melatonin

Melatonin is secreted by the pineal gland, and its secretion regulates and modifies circadian rhythms and sleep [39]. Plasma melatonin levels are decreased after surgery and in hospitalized patients [40]. In a meta-analysis, melatonin given as premedication in adults reduces preoperative anxiety when compared with placebo and is equally effective when compared with midazolam [41]. In a small sample size study of patients undergoing prostatectomy, preoperative melatonin enhanced sleep quality, decreased pain scores and tramadol consumption, but produced sedation during the early postoperative period [42]. For patients after breast cancer surgery, melatonin administration improves sleep quality without producing significant side effects [43–45].

Dexmedetomidine

Dexmedetomidine is a selective $\alpha_2$ adrenoceptor agonist with both sedative and analgesic properties [46]. Unlike other sedative agents, dexmedetomidine exerts its sedative effects through an endogenous sleep-promoting pathway and produces a N2 sleep-like state [47]. In mechanically ventilated ICU patients, nighttime infusion of sedative dose of dexmedetomidine preserved the day–night cycle of sleep and improved the sleep architecture by increasing sleep efficiency and stage N2 sleep [48,49]. In nonmechanically ventilated elderly patients who were admitted to the ICU after surgery, low-dose dexmedetomidine infusion (0.1 $\mu$g/kg/h) during the night after surgery prolonged total sleep time, increased N2 (and decreased N1) sleep, and improved subjective sleep quality [50].

Effects of sleep promotion on patients’ outcomes after surgery

Sleep-promotion is helpful for recovery of postoperative patients. In ICU patients, improving sleep with ear plugs and eye mask reduces the incidence of delirium [35,51], further demonstrating the correlation between sleep disturbance and delirium development. In a recent large sample size study, 700 patients (≥65 year) who were admitted to ICU after surgery randomly received either low-dose dexmedetomidine infusion (0.1 $\mu$g/kg/h) or placebo during the night after surgery. The results showed that low-dose dexmedetomidine infusion decreased the prevalences of delirium on postoperative days 1–3, which was in accordance with the improved subjective sleep quality during the 3 nights of the same period. Low-dose dexmedetomidine infusion also reduces nondelirium complications [52]. For patients after orthopedic surgery, use of zolpidem reduces postoperative pain, fatigue, and narcotic consumption [53], and improves quality of life [54]. Long-term effects of sleep-promotion therapy remain to be determined.

CONCLUSION

Sleep disturbances frequently occur after surgery, especially major surgery. Factors associated with the occurrence of postoperative sleep disturbances include old age, preoperative comorbidity, type of anesthesia, severity of surgical trauma, postoperative pain, environment stress, as well as other factors leading to discomfort of patients. Development of sleep disturbances produces harmful effects on postoperative patients, that is, higher risk of delirium, increased sensitivity to pain, more cardiovascular events, and poorer recovery. Both nonpharmacological and pharmacological measures can be used to improve postoperative sleep and may be helpful for postoperative recovery. Long-term effects of sleep promotion therapy deserve further study.

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REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:

** of outstanding interest

1. Arell J, Elmpst D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. Br Med J 1985; 290:1029–1032.
2. Knii RL, Moote CA, Skinner MI, Rose EA. Anesthesia with abdominal surgery leads to increased REM sleep during the first postoperative week. Anaesthesiology 1990; 73:52–61.
3. Dette F, Cassel W, Urban F, et al. Occurrence of rapid eye movement sleep deprivation after surgery under regional anesthesia. Anesth Analg 2015; 116:939–943.
4. Kjolhede P, Langstrom P, Nilsson P, et al. The impact of quality of sleep on recovery from fast-track abdominal hysterection. J Clin Sleep Med 2012; 8:395–402.
5. Fernandez NM, Nielde LD, Popel N, et al. Symptoms of disturbed sleep predict major adverse cardiac events after percutaneous coronary intervention. Can J Cardiol 2014; 30:118–124.
6. McNamar PA, Johnson P, McLaren D, et al. REM and NREM sleep mentation. Int Rev Neurobiol 2010; 92:69–86.
7. Elliott R, McRae S, Cistulli P. The quality and duration of sleep in the intensive care setting: an integrative review. Int J Nurs Stud 2011; 48:384–400.
8. Chung F, Liao P, Yegneswaran B, et al. Postoperative changes in sleep-disordered breathing and sleep architecture in patients with obstructive sleep apnea. Anesthesiology 2014; 120:287–298.
9. Chung F, Liao P, Elsahd H, et al. Factors associated with postoperative exacerbation of sleep-disordered breathing. Anesthesiology 2014; 120:299–311.
10. Rosenberg-Adamsen S, Kehlet H, Dodd C, Rosenberg J. Postoperative sleep disturbances: mechanisms and clinical implications. Br J Anaesth 1996; 76:552–559.
11. Sterniczuk R, Rusak B, Rockwood K. Sleep disturbance in older ICU patients. Clin Intensive Care 2014; 9:69–97.
12. Yilmaz S, Aksoy E, Dogan T, et al. Angina severity predicts worse sleep quality after coronary artery bypass grafting. Perfusion 2016; 31:471–476.
13. Cronin AJ, Kefer JC, Davies MF, et al. Postoperative sleep disturbance: influences of opioids and pain in humans. Sleep 2001; 24:39–44.
14. Krenk L, Jønner P, Kehlet H. Sleep disturbances after fast-track hip and knee arthroplasty. Br J Anaesth 2012; 109:769–775.
15. Rosenberg-Adamsen S, Skarbye M, Wildschiotz G, et al. Sleep after laparoscopic cholecystectomy. Br J Anaesth 1996; 77:572–579.
16. Hansen MV, Madsen MT, Wildschiotz G, et al. Sleep disturbances and changes in urinary 6-sulphatoxymelatonin levels in patients with breast cancer undergoing lumpectomy. Acta Anaesthesiol Scand 2013; 57:1146–1153.
17. Dolan R, Hur J, Tiwari N, et al. A prospective analysis of sleep deprivation and disturbance in surgical patients. Ann Med Surg 2016; 1:1–5.
18. Arell J, Elmpst D, Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. Br Med J 1985; 290:1029–1032.
19. Xie H, Kang J, Mills GH. Clinical review: the impact of noise on patients’ sleep and the effectiveness of noise reduction strategies in intensive care units. Crit Care 2009; 13:208.
20. Christensen M. Noise levels in a general surgical ward: a descriptive study. J Clin Nurs 2005; 14:158–164.
21. Leung JM, Sands LP, Newman S, et al. Preoperative sleep disruption and postoperative delirium. J Clin Sleep Med 2015; 11:907–913.
22. Todd OM, Geirich L, MacLulich AM, et al. Sleep disruption at home as an independent risk factor for postoperative delirium. J Am Geriatr Soc 2017; 65:949–957.
23. Fink BJ, Riviello SK, Cox EA, et al. Obstructive sleep apnea and incidence of postoperative delirium after elective knee replacement in the nondemented elderly. Anesthesiology 2012; 116:788–796.
24. Slator CG, Goy ER, O’Hearn DJ, et al. Sleep quality and its association with delirium among veterans enrolled in hospice. Am J Geriatr Psychiatry 2012; 20:317–328.
25. Raymond I, Ancoli-Israel S, Chouinere M. Sleep disturbances, pain and analgesia in adults hospitalized for burn injuries. Sleep Med 2004; 5:551–559.
26. Raymond I, Nelsen TA, Lavigne G, et al. Quality of sleep and its daily relationship to pain intensity in hospitalized adult burn patients. Pain 2001; 92:381–388.
27. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain 2013; 14:1593–1552.
28. Luke YK, Brown JW, Kwok CS, et al. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2012; 5:720–728.
29. Cremers-Smith JK, Millington K, Slenders E, et al. Sleep disruptions mediate the relationship between early postoperative pain and later functioning following total knee replacement surgery. J Pain Behav Med 2009; 29:215–222.
30. Enlyma MM, Ozdemir C, Yurtman F, et al. Quality of sleep and change in urinary 6-sulphatoxymelatonin levels in patients with breast cancer undergoing lumpectomy. Acta Anaesthesiol Scand 2013; 57:1146–1153.
31. Kachueh H, Ameli J, Taheri S, et al. Sleep quality and its correlates in renal transplant patients. Transplant Proc 2007; 39:1095–1097.
32. Molnar MZ, Novak M, Musci I. Sleep disorders and quality of life in renal transplant recipients. Int Urol Nephrol 2009; 41:373–382.
33. Fontana CJ, Pitigliano LJ. Sleep deprivation among critical care patients. Crit Care Nurs Q 2010; 33:75–81.
34. Li SY, Wang TJ, Vivenne Wu SF, et al. Efficacy of controlling night-time noise and activities to improve patients’ sleep quality in a surgical intensive care unit. J Clin Nurs 2011; 20:396–407.
35. Hu RF, Jiang XY, Chen J, et al. Nonpharmacological interventions for sleep promotion in the intensive care unit. Cochrane Database Syst Rev 2015; Cd008805.
36. Kanji S, Mera A, Hutton B, et al. Pharmacological interventions to improve sleep in hospitalised adults: a systematic review. BMJ Open 2016; 6:e012108.
37. The systematic review evaluated the comparative efficacy and safety of pharamacological interventions used for sleep in hospitalised patients. The authors concluded that there is insufficient evidence to suggest that pharmacotherapy improves the quality or quantity of sleep in hospitalised patients suffering from poor sleep.
38. Summer B. The sleep-wake cycle and sleeping pills. Physiol Behav 2007; 90:285–293.
39. Krenk L, Jønner P, Kehlet H. Postoperative sleep disturbances after zolpidem treatment in fast-track hip and knee replacement. J Clin Sleep Med 2014; 10:321–326.
40. Arendt J. Melatonin, circadian rhythms, and sleep. N Engl J Med 2000; 343:1114–1116.
41. Baskett JJ, Cockrem JF, Todd MA. Melatonin levels in hospitalised elderly patients: a comparison with community based volunteers. Age Ageing 1991; 20:430–434.
42. Hansen MV, Halladin NL, Rosenberg J, et al. Melatonin for pre and postoperative anxiety in adults. Cochrane Database Syst Rev 2015; Cd008961.
43. Borazon H, Turner S, Yalac N, et al. Effects of preoperative oral melatonin medication on postoperative analgesia, sleep quality, and sedation in patients undergoing elective prostatectomy: a randomized clinical trial. J Anesth 2010; 24:155–160.
44. Chen WY, Globbie-Hurder A, Gartman K, et al. A randomized, placebo-controlled trial of melatonin on breast cancer survivors: impact on sleep, mood, and hot flashes. Breast Cancer Res Treat 2014; 145:381–388.
45. Hansen MV, Madsen MT, Andersen LT, et al. Effect of melatonin on cognitive function and sleep in relation to breast cancer surgery: a randomized, double-blind, placebo-controlled trial. Int J Breast Cancer 2014; 2014:146531.
46. Madsen MT, Hansen MV, Andersen LT, et al. Effect of melatonin on sleep in the perioperative period after breast cancer surgery: a randomized, double-blind, placebo-controlled trial. J Clin Sleep Med 2016; 12:225–233.
47. Reardon DP, Anger KE, Adams CD, Szumita PM. Role of dexmedetomidine in improving postoperative sleep quality in critically ill patients: a pilot study. Anaesthesiology 2014; 121:801–807.
Wu XH, Cui F, Zhang C, et al. Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: a pilot randomized controlled trial. Anesthesiology 2016; 125:979–991. The pilot randomized controlled trial investigated the effect of low-dose dexmedetomidine infusion in improving sleep architecture in nonmechanically ventilated elderly patients in the ICU after surgery. The authors reported that prophylactic dexmedetomidine infusion improved the overall sleep quality.

Litton E, Carnegie V, Elliott R, Webb SA. The efficacy of earplugs as a sleep hygiene strategy for reducing delirium in the ICU: a systematic review and meta-analysis. Crit Care Med 2016; 44:992–999. The meta-analysis included nine intervention studies with 1455 ICU patients. The authors concluded that use of earplugs, either in isolation or as part of a bundle of sleep hygiene improvement, is associated with reduced risk of delirium.

Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after noncardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 2016; 388:1893–1902. The randomized controlled trial demonstrated that, for elderly patients admitted to the ICU after noncardiac surgery, prophylactic low-dose dexmedetomidine decreases the occurrence of delirium during the first 7 days after surgery.

Tashjian RZ, Banerjee R, Bradley MP, et al. Zolpidem reduces postoperative pain, fatigue, and narcotic consumption following knee arthroscopy: a prospective randomized placebo-controlled double-blinded study. J Knee Surg 2006; 19:105–111.

Gong L, Wang Z, Fan D. Sleep quality effects recovery after total knee arthroplasty (TKA) – a randomized, double-blind, controlled study. J Arthroplasty 2015; 30:1897–1901.