

Cardiopulmonary adverse events during procedural sedation in patients with obstructive sleep apnoea: a systematic review and meta-analysis

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Abstract

Obstructive sleep apnoea in surgical patients is associated with cardiac and respiratory complications in the peri-operative period. Agents commonly administered for procedural sedation, such as hypnotic-sedatives, benzodiazepines and opioids can cause respiratory depression and muscle relaxation, and lead to loss of upper airway patency and finally to airway collapse. However, there is limited evidence supporting an increased risk of peri-operative adverse events in the obstructive sleep apnoea population receiving procedural sedation and analgesia for diagnostic or therapeutic medical procedures. The objective of the systematic review presented in this thesis was to identify, assess and synthesise the available evidence on cardiac and respiratory complications during propofol, midazolam and fentanyl sedation administration and diagnosed obstructive sleep apnoea.

A comprehensive search for relevant studies published in the English language was conducted using PubMed/MEDLINE, CINAHL, EMBASE, Scopus and relevant sources of grey literature. Four thousand and twenty eight citations were screened to determine eligibility with 80 records retrieved for detailed examination of the full text. Five studies matched the eligibility criteria for the review and underwent critical appraisal by two reviewers using the Joanna Briggs Institute – Meta Analysis of Statistics, Assessment and Review Instrument. Where possible, data was analysed using RevMan 5.3 software using a random effects model.

Five studies reported on sedation associated complications in patients with confirmed obstructive sleep apnoea undergoing gastrointestinal endoscopy. No studies conducted on patients undergoing other procedures were identified. The total number of participants included in the studies was 1826 (n=1079, obstructive sleep apnoea group; n=747, non-obstructive sleep apnoea group). Meta-analysis revealed no significant association between diagnosis of obstructive sleep apnoea and cardiopulmonary complications during procedural sedation with midazolam, fentanyl or propofol, including oxygen desaturation odds ratio (OR) 0.84 (95% CI: 0.47-1.47; five studies); hypotension OR 0.95 (95% CI: 0.55-1.63; three studies), bradycardia OR 0.85 (95% CI: 0.58-1.25; two studies); tachycardia OR

0.74 (95% CI: 0.43-1.29; two studies) and complications requiring intervention OR 1.23 (95% CI: 0.64-2.37; four studies).

Despite the lack of association between confirmed obstructive sleep apnoea and increased risk of cardiopulmonary adverse events, the limitations arising from the multiple gaps in the reporting of the studies (notably with regard to patient characteristics and outcome measurements) and the representativeness of the OSA population (OSA patients undergoing only endoscopic procedures), limit the extent to which the results can be generalised.

Declaration

I, Ella Gagolkina, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Ella Gagolkina

October 2016

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1. Introduction

1.1 Context of the review

Obstructive sleep apnoea (OSA) is a common medical condition and an important health issue. Obstructive sleep apnoea is associated with impaired cognition (Saunamaki and Jehkonen, 2007, Bawden et al., 2011), poor quality of life (Finn et al., 1998, Sharafkhaneh et al., 2005) and an increased risk for car accidents (Stradling, 2008, Tregear et al., 2009). Obstructive sleep apnoea has been found to increase the risk of cardiovascular disease (Gottlieb et al., 2010), hypertension (Phillips and Cistulli, 2006), cardiac arrhythmias (Shepard, 1992) and cerebrovascular disease (Yaggi et al., 2005) and is linked to metabolic impairments such as glucose intolerance, insulin resistance, and type 2 diabetes (Briancon-Marjollet et al., 2015).

Patients with OSA are also at an increased risk for peri-operative respiratory or cardiac complications (Gupta et al., 2001, Hwang et al., 2008, Liao et al., 2009, Kurrek et al., 2011, Memtsoudis et al., 2011) including post-operative oxygen desaturation, respiratory failure, cardiac events, as well as unexpected admissions to the intensive care unit (Gupta et al., 2001, Mutter et al., 2014). A study by Memtsoudis et al., (2011), which analysed data from a large national (United States) inpatient sample, identified sleep apnoea as an independent risk factor for peri-operative adverse outcomes. The study found that patients with sleep apnoea developed pulmonary complications more often than their matched controls. For example, after orthopaedic procedures, aspiration pneumonia was identified in 1.18% of sleep apnoea patients compared to 0.84% of controls, and 3.99% of sleep apnoea patients required intubation/mechanical ventilation compared to 0.79% of controls (Memtsoudis et al., 2011). Similarly, a systematic review by Ankichetty and colleagues (2011) and two recently published meta-analyses (Kaw et al., 2012, Gaddam et al., 2014) both investigating the association between OSA and post-operative outcomes found that surgical patients with OSA were at increased risk for peri-operative respiratory or cardiac complications following non-upper airway surgery (Ankichetty et al., 2011, Kaw et al., 2012, Gaddam et al., 2014).

Peri-operatively administered sedative-hypnotic anaesthetic and analgesic agents can amplify respiratory problems and exacerbate OSA, resulting in complications during the post-operative period (Chung et al., 2014, McEntire et al., 2014, Mulier, 2016). One of the earliest accounts of OSA related complications in the post-operative period was published in 1997 by Ostermeier and colleagues who reported three fatal cases of respiratory arrest following epidural opioid administration to patients with sleep apnoea during the post-operative period (Ostermeier et al., 1997). However, it was a subsequent case-control study by Gupta and colleagues (2001) that demonstrated a higher rate of adverse post-operative outcomes such as delirium, episodic desaturations, acute hypercapnia, myocardial infarction or ischaemia, and cardiac arrhythmias associated with clinical symptoms, occurred in patients diagnosed with OSA than in non-OSA patients who underwent general anaesthesia for hip or knee replacement. The authors also reported a significantly longer duration of hospital stay for patients with OSA compared to those without OSA (Gupta et al., 2001). The alarming number of cardiovascular complications in orthopaedic patients with OSA demonstrated in the study by Gupta and co-workers (2001) raised awareness in the medical community of the risks associated with OSA and highlighted that peri-operative complications should be anticipated in patients diagnosed with OSA.

Although the clinical importance of underlying OSA when administering general anaesthetic to surgical patients has been known for some time, the safety of procedural sedation administration (PSA) in the OSA population is still not clear, despite it being an important and confronting topic. For clinicians administering sedation, the question of PSA safety arises on a daily basis as the number of patients presenting with OSA continues to increase. The uncertainty in clinical practice is exacerbated by the regular observation (author's unpublished observation) that some patients with OSA develop unwanted adverse events with PSA during the peri-operative period while others do not.

Not all OSA patients who present for surgical treatment are aware of their condition and consequently, are able to warn their healthcare providers about their disorder. Despite increased awareness of the condition and the availability of

screening (e.g., STOP-BANG questionnaire) and diagnostic tools (e.g. polysomnography), OSA often goes unsuspected or passes undetected when a patient is admitted to hospital for diagnostic or therapeutic medical procedures. However findings from studies published in this field (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015) and practitioners' clinical observations continually raise questions about the safety of sedation administration to patients with OSA, and given the high prevalence of undiagnosed sleep respiratory disorder, whether the clinical safety of the patient is compromised if OSA is not identified. (Detailed presentation on prevalence of undiagnosed OSA in surgical population is described in Section 1.7).

Nevertheless, there is limited and contradictory evidence that OSA patients receiving sedation for gastro-intestinal (GI) procedures are at increased risk for peri-operative side effects. For example, a systematic review and a meta-analysis published after the commencement of the research presented in this thesis, (Gaddam et al., 2015) sought to determine whether the presence of OSA increased the incidence of post-GI endoscopy complications. The review included seven studies involving patients either diagnosed with OSA or patients at high risk of OSA. The reviewers concluded there were no significant association between patients diagnosed with OSA or at high risk of OSA, and post-GI endoscopy complications such as hypoxaemia, respiratory distress, variations in blood pressure or heart rate, bradypnoea, or the need for significant interventions. In other words, there was no significant increase in the rate of adverse events in patients with OSA or those at high risk for OSA compared to patients without OSA who were undergoing GI procedures with sedation (Gaddam et al., 2015). In contrast, current knowledge and safety guidelines encourage the use of extra caution when general anaesthetic or sedation are indicated for procedures with patients who are at high risk of OSA or have been diagnosed with the disorder (Meoli et al., 2003, Practice Guidelines, 2014).

The inclusion criteria for the recently published systematic review was similar to the inclusion criteria originally developed in *a priori* protocol (Gagolkina et al., 2014, Appendix 1) for the work presented in this thesis. However, the research presented in this thesis was different from the review by Gaddam et al., (2015) in

that it was not limited to GI endoscopies and only patients with confirmed OSA (not those at high risk) were included in the OSA group. Careful examination of the included studies was made to ensure only studies that used the gold standard polysomnography (PSG) for diagnosing OSA (see Section 1.3.1) were included, to allow for the examination of differences, if any, between confirmed OSA and without OSA patients. In summary, the present review was restricted to identifying and assessing the available evidence on the incidence of adverse cardiopulmonary outcomes of fentanyl, midazolam and propofol administered to patients with confirmed OSA undertaking therapeutic and/or diagnostic procedures under sedation.

Chapter 1 of this thesis outlines 1) pathophysiological mechanisms of OSA, clinical manifestations and the risk factors for OSA; 2) the concept of procedural sedation and 3) reviews sedative agents propofol, fentanyl and midazolam. Safety of sedation administration is also discussed in this chapter.

1.2 Pathophysiology of obstructive sleep apnoea in adults

The pathophysiology of OSA is complex and can vary between individuals. This section presents a brief summary of the potential mechanisms involved in the development of OSA, including during general anaesthesia.

1.2.1 Upper airway anatomy

The human upper airway (pharynx) is a complicated, multipurpose structure that forms a passage for the movement of air for respiration, and is involved in physiological functions such as speech and swallowing (Ayappa and Rapoport, 2003). There are more than 20 muscles that surround the upper airway, and these are actively involved in the constriction or dilatation of the airway lumen (Ayappa and Rapoport, 2003). These muscles regulate the position of the soft palate, tongue, hyoid apparatus and the pharyngeal walls, and interact in a complex manner to determine the patency of the airway (Ayappa and Rapoport, 2003). The airway lacks a bony or structural support; therefore, the shape and size of the airway depends on the position of the soft tissue structure that comprises the tongue, soft palate and oropharynx. Absence of any bony protection of the airway from external forces explains the vulnerability of the pharyngeal structure and predisposes the upper airway to collapse (Ayappa and Rapoport, 2003).

1.2.2 Patency of the upper airway

Pharyngeal muscle tone maintains the airway structure, keeps the airway open, and allows undisturbed breathing. The oropharyngeal dilator and abductor muscles are responsible for the stability and patency of the upper airway during breathing and their action is coordinated with each inspiration (Deegan and McNicholas, 1995). The patency of the upper airway depends on a balance between the forces that promote airway collapse and predominant forces that promote airway patency. When the force produced by the pharyngeal muscles to keep the airway patent is exceeded by negative airway pressure produced by the inspiratory movement of the diaphragm and intercostal muscles, the pharynx is subject to narrowing or collapse (Deegan and McNicholas, 1995).

Fat deposition within the walls of the pharynx narrows the airways and changes the shape of the pharynx. In obese people, the upper airway is compressed externally by this extraluminal fat mass, that increases extraluminal pressure and compromises airway patency (Benumof, 2002). Negative pressure ventilation (inhaling a breath) combined with pharyngeal extraluminal positive pressure together promotes airway collapse. In addition to obesity, these forces contributing to airway collapse may also be exaggerated by obstructive lesions of the upper airway (e.g. enlarged tonsils) and small mandibular size (Deegan and McNicholas, 1995).

1.2.3 Sleep and breathing

Sleep is an important natural physiological process and is an essential part of life. Although the nature of sleep remains unclear, good quality sleep is fundamental to our physical and emotional wellbeing. Disordered breathing can significantly disturb sleep, resulting in frequent arousals and sleep fragmentation (Berry and Gleeson, 1997). Fragmented sleep is responsible for the daytime somnolence in people affected by OSA (Berry and Gleeson, 1997). The detailed mechanism of airway obstruction during sleep in OSA is described in Section 1.2.4.

The phenomenon of sleep can be described as a state of rousable unconsciousness, which is marked by distinct phases of brainwave activity and variations in muscle tone. On the basis of electrophysiological measurements of brain waves, sleep can be divided into non-rapid eye movement and rapid eye

movement (Dempsey et al., 1996). Breathing control during sleep is unique for each state. According to the particular sleep state, changes in respiratory drive, breathing pattern and various effects on the mechanics of breathing occur during sleep (Dempsey et al., 1996). The mechanism of respiratory system control during sleep is very complex and a discussion of the issues associated with it is beyond the scope of this thesis. In summary, it is important that respiration is maintained at a level to sustain life and physiological health. This includes control over the rate and depth of breathing and the maintenance of airways to allow adequate gas exchange within the lungs.

1.2.4 Sleep and obstructive sleep apnoea

Maintaining patency of the airways during sleep is a complex interrelationship between neural control of pharyngeal muscle tone and the pharyngeal structure (Horner, 2008). During sleep in healthy individuals, the pharyngeal muscle tone prevents the airway from collapse. Figure 1.1 demonstrates the patency of airway and the site of obstruction during sleep in OSA and non-OSA.

In patients with OSA, the neural input to the pharyngeal dilator muscle is diminished with loss of wakefulness during sleep. This in return, results in the loss of the pharyngeal muscle tone. At the same time, the soft tissues of the pharynx, such as the tongue and soft palate collapse on the pharyngeal airway under gravitational forces (Horner, 2008). Recurrent pharyngeal collapse during sleep causes periods of reduction (hypopnoea) or complete cessation (apnoea) of airflow to the lungs (definition of hypopnoea and apnoea provided in Section 1.3). The obstruction to airflow remains present until sleep is interrupted, the individual awakens, and muscle tone is restored. Repeated episodes of these events alter sleep architecture and sleep duration. Sleep disruptions result in daytime somnolence and organ system dysfunction (Horner, 2008).

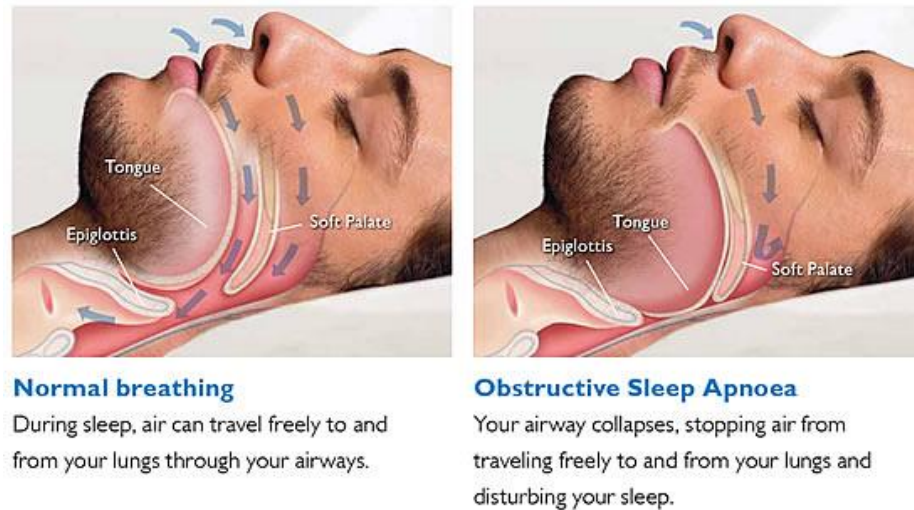


Figure 1.1 Patency of the airway and the site of obstruction during sleep in non-OSA and OSA

apnea.jpg accessed from

www.eleceng.adelaide.edu.au/students/wiki/projects/index.php/File:Apnea.jpg

1.2.5 Effect of body position on obstructive sleep apnoea

Body position influences the severity and frequency of respiratory events in individuals with OSA. Positional OSA is when the respiratory disturbance index (defined in Section 1.3) is twice as high in the supine position (i.e. the patient is asleep on their back), as in the lateral position (i.e. the patient is asleep on their side) (Cartwright et al., 1991). Later PSG studies (Oksenberg et al., 1997) as well as drug-induced sleep endoscopy studies (Lee et al., 2015) on OSA patients confirmed that the rate of occurrence of airway obstruction leading to apnoea is less when a patient is asleep in a lateral position compared to when the same patient is asleep in a supine position. Similar to the lateral position, a prone position (i.e. face down) reduces the apnoea-hypopnoea index (defined in Section 1.3) (Bidarian-Moniri et al., 2015, Afrashi and Ucar, 2015). Therefore, lateral and prone positions during sleep can be considered as the equivalent of passive airway manipulation and are considered to be the optimal positions during sleep.

1.2.6 Upper airway obstruction during anaesthesia

When established, anaesthesia is a state of unrousable unconsciousness. The effects of anaesthesia on airway muscular tone are similar to those described for OSA, so much so, that the homogenous and profound loss of pharyngeal muscle tone may, if left untreated, result in asphyxia (Hillman et al., 2003, Hillman et al.,

2004, Jain and Dhand, 2004). Sedative and anaesthetic medications produce a dose dependent decrease of pharyngeal tone, and depression of the arousal responses to hypoxia, hypercarbia and airway obstruction, that usually protect against asphyxia (Loadsman and Hillman, 2001). Therefore, the maintenance of airway patency during sleep is a shared concern among anaesthetists and sleep physicians, as both anaesthesia and sleep predispose the upper airway to obstruction, mainly due to a loss of a wakeful pharyngeal tone (Hillman et al., 2004). Eastwood and co-workers (2005) demonstrated that increasing depth of sedation or anaesthesia when using the anaesthetic/hypnotic drug propofol was positively associated with increased upper airway collapsibility, which was associated with decreased genioglossus muscle inspiratory activity (Eastwood et al., 2005). As the two states of anaesthesia and sleep can be compared, it is possible that the mechanism of airway obstruction during sleep and whilst under anaesthesia is similar in nature.

1.3 Defining obstructive sleep apnoea

The Adult OSA Task Force of the American Academy of Sleep Medicine (AASM) developed standard definitions of abnormal respiratory events during sleep. The following terminology applies when defining OSA:

- Apnoea is an absence of airflow through the airways despite continued or increased respiratory effort; an event that lasts for at least 10 seconds.
- Hypopnoea is a reduction of airflow through the airways, with the drop of signal by 30% when measured with a hypopnoea sensor and the presence of a >4% desaturation event from baseline; an event that lasts for at least 10 seconds.
- Hypoventilation is reduced normal respiration as demonstrated by increased pCO₂ value (>45 mmHg) on capnography, measured immediately after awakening from sleep.
- Respiratory effort related arousals are a sequence of breaths lasting at least 10 seconds, characterised by increased respiratory effort or flattening of the nasal pressure waveform leading to arousal from sleep (Berry et al., 2012, pp.605-606).

Obstructive sleep apnoea is characterised by abnormal breathing patterns

involving a combination of apnoea, hypopnoea, hypoventilation and respiratory effort related arousals during sleep. According to the International Classification of Sleep Disorders - Third Edition, (Sateia, 2014, p.1389) diagnosis of OSA can be defined as follows:

- There are five or more obstructive respiratory events (as defined in the AASM guidelines) per hour of sleep in a patient present with:
 - signs or symptoms of unexplainable daytime sleepiness, fatigue or insomnias; snoring, or breathing interruptions observed by the bed partner, or
 - diagnosis of one or more of the following co-morbidities: hypertension, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, type 2 diabetes mellitus, mood disorder or cognitive dysfunction.
- Alternatively, the diagnosis of OSA can be based on the presence of 15 or more obstructive respiratory events (confirmed by an overnight sleep study) per hour of sleep in the absence of the listed above symptoms or co-morbidities.

Severity of OSA is based on the frequency of the obstructive respiratory events per hour of sleep according to the results of overnight monitoring (AASM Report, 1999). The sum of these events per hour of sleep is referred to as the apnoea/hypopnoea index (AHI) (also known as the respiratory disturbance index (RDI) (see Table 1.1).

Table 1.1 Sleep related obstructive events

Number of apnoea/hypopnoea events per hour of sleep	OSA Rating
<5	Normal
5 to 15	Mild
15 to 30	Moderate
>30	Severe

OSA = obstructive sleep apnoea.

Diagnosis of OSA is a complex process. While many people suffer from poor quality sleep and complain of being tired and sleepy during the day, not everyone

will develop the condition. A decision to formally investigate for OSA is based on an evaluation of the patient's medical history, physical examination and daytime symptoms. Often it is a bed partner who first arouses suspicion of OSA by reporting that they have witnessed apnoeic episodes. An individual's risk factors for OSA, such as obesity, age, family history and body habitus (e.g. cigarette smoking, alcohol intake) are also considered (see Section 1.8). Polysomnography in clinical settings and home sleep apnoea testing (HSAT) with a portable monitor are the methods used for the objective recording of sleep patterns and the measurement of sleep quality (Epstein et al., 2009). A definite diagnosis of OSA is based on an assessment of both (1) the sleep evaluation and breathing during sleep, and (2) the measurements of daytime symptoms (e.g. sleepiness). More information on PSG and HSAT is provided in Sections 1.3.1 and 1.3.2. Drug induced sleep endoscopy (DISE), a procedure designed for examination of the airway under pharmacologically induced sleep, is also described in this chapter (see Section 1.3.4).

In clinical practice, it is often the case that patients present for a medical procedure who have never been formally screened for OSA or assessed for risk of OSA. During peri-operative assessment, patient's clinical features and medical history may force the clinician to make a presumptive diagnosis of OSA. Recently published guidelines of peri-operative management of the obese surgical patients, recommend that the safest principle is to assume that all obese patients may have a degree of sleep disordered breathing (Nightingale et al., 2015). The same principle should be applied with procedural sedation and cautious management should be employed if OSA is suspected. To assist clinicians with risk assessment for OSA in pre-operative settings, various screening questionnaires and clinical prediction models such as the STOP-BANG instrument (Chung et al., 2008), Multiple Sleep Latency Test (Moldofsky, 1992, Arand et al., 2005) and the Epworth Sleepiness Scale (Johns, M., 1993) have been developed. Detailed description of the STOP-BANG tool developed to determine the severity of OSA and predict risk of OSA is presented in the Section 1.3.3 and in Appendix 2.

1.3.1 Polysomnography (PSG)

Currently, PSG is a comprehensive, reliable and trusted sleep study test that is considered to be the gold standard for the diagnosis of OSA. Polysomnography involves an overnight stay in a sleep laboratory with multichannel monitoring and observation of complex motor behaviour during sleep, which involves the recording of important physiological parameters as brain function (electroencephalogram), eye movements (electro-oculogram), heart rate, oxygen saturation (pulse oximetry), nasal airflow and intensity of snoring, chin and leg electromyography and respiration with abdominal and thoracic respiratory effort (Young et al., 2002a). Using AHI, PSG determines the standard index of disease in disease severity (discussed in Section 1.3 and Table 1.1) and can also determine the positive airway pressure required for the treatment of OSA (Ontario Assessment, 2006). Despite its reliability, PSG is a labour intensive, time consuming and expensive test (Ontario Assessment, 2006). Consequently, it is often impractical to refer all patients to undertake the test and therefore difficulties associated with diagnosing OSA are still a present concern.

1.3.2 Home sleep apnoea testing (HSAT)

Portable monitoring for the diagnosis of OSA is an alternative to PSG. Home sleep apnoea testing is indicated for the evaluation of highly suspected OSA and in assessing treatment of OSA (Collop et al., 2007, Epstein et al., 2009). According to the AASM guidelines, HSAT should be performed in conjunction with a comprehensive sleep evaluation that must be supervised by a sleep specialist (AASM Report, 1999). The major advantages of HSAT are its convenience, as attendance by a sleep technician is not required, (the test can be performed at home or in a hospital room) and its low cost. The major disadvantage of the HSAT is the potential for the results to be misinterpreted as fewer physiological parameters are measured compared to PSG (Collop et al., 2007, Epstein et al., 2009).

1.3.3 STOP-BANG questionnaire

The STOP-BANG is a user-friendly screening questionnaire (Appendix 2) that was designed by anaesthetists and sleep physicians in a binary (yes/no) format to help screen and identify patients at high risk for OSA (Chung et al., 2008). The

tool is composed of eight questions that assess the most common risk factors for OSA. Four questions comprise the STOP component of the questionnaire and focus on snoring; tiredness during the daytime; observed cessation of breathing during sleep; and blood pressure (i.e. hypertension) (Questions 1-4, Appendix 2). A further four questions comprise the BANG component and focus on individuals' body mass index (BMI); age; neck circumference; and gender (Questions 5-8, Appendix 2).

The screening tool was validated on 1,875 surgical patients and showed a high sensitivity in predicting moderate to severe OSA (AHI ≥ 15 : 92.9%, AHI ≥ 30 : 100%) (Chung et al., 2008). A score comprising three or more 'yes' answers has a sensitivity of 83.6% for patients who have an AHI greater than five on a PSG test; sensitivity increases to 92.9% for patients with an AHI of more than 15, which correlates with a high probability of moderate to severe OSA (Chung et al., 2008). While the STOP-BANG instrument is highly accurate in detecting severe OSA (AHI ≥ 15), it is not as reliable in predicting mild to moderate OSA (Chung et al., 2008). Although the STOP-BANG is used to assess an individual's risk for OSA, it does not provide the clinical basis for a confirmed diagnosis of OSA. Therefore, obtaining a patient's medical history and conducting a physical examination remain the most reliable methods for detecting and diagnosing OSA during pre-operative assessment, when PSG results are not available.

1.3.4 Drug induced sleep endoscopy (DISE) for evaluation of obstructive sleep apnoea

Drug induced sleep endoscopy (DISE), also called sleep nasoendoscopy is a procedure designed for the examination of the airway under conditions of spontaneous ventilation and also pharmacologically induced sleep. This procedure is commonly utilised to study the pathophysiology of OSA but not for the initial diagnosis of OSA. Originally described by Croft and Pringle (1991), the procedure is indicated for patients with OSA and is a valid addition in the diagnostic workup of OSA when surgical treatment is considered.

Drug induced sleep endoscopy is performed in an operating room with the patient placed in a supine position with standard monitoring equipment. Sedation with propofol or midazolam is used to induce an airway obstruction in patients with

OSA to facilitate an upper airway analysis, so the exact location and mechanism of upper airway collapse can be established (Croft and Pringle, 1991). Following sedation administration, the bronchoscope is passed via the nares, allowing images and a video recording of the anatomic site(s) of obstruction (Borek et al., 2012). On the basis of the DISE results, subsequent surgical treatment plans can be tailored to each patient.

1.4 Recognition of obstructive sleep apnoea as a health issue

Despite the characteristics of OSA being clearly described by Broadbent (and frequently quoted in modern publications) as early as 1877 (Lavie, 1984), it has taken a century for the condition to be recognised as a serious health issue. It is not always an easy to establish the presence of the breathing disorder. Although OSA is associated with disturbed sleep at night, quite often people affected by the disorder feel fine when they are awake during the day. Conversely, OSA can also manifest in debilitating day-time symptoms such as sleepiness and fatigue. Unfortunately, patients and clinicians tend to attribute these symptoms to stress, old age, or even consider them to be a normal part of life, and as a consequence, medical assessment and examination are not considered further. These are a few of the likely reasons as to why it took many years for OSA to be recognised as a medical issue.

1.5 Clinical manifestations of obstructive sleep apnoea

1.5.1 Snoring

Snoring is a manifestation of partial airway obstruction. Loud snoring is a typical feature of OSA and occurs due to the vibration of the soft tissues of the pharynx, soft palate and uvula while air is accelerating through these structures (Ayappa and Rapoport, 2003). Almost half of all people who snore have some degree of OSA and the majority of people diagnosed with OSA snore to some degree (Barthel and Strome, 1999); however, loud snoring on its own is not confirmation of OSA.

1.5.2 Daytime sleepiness

Daytime sleepiness, or an inability to stay awake during the wakefulness segment of the sleep-awake cycle, is another common symptom of OSA and is a result of

fragmented sleep due to frequent arousals (Schlosshan and Elliott, 2004). Often described as fatigue, tiredness or lack of energy, daytime sleepiness is an important consequence of OSA. Sleepiness can be assessed by using a variety of instruments that measure the probability of falling asleep in everyday situations (e.g. watching TV, reading, talking to someone, driving the car, etc.) (Johns, 1993). The Epworth Sleepiness Scale and Stanford Sleepiness Scale are examples of questionnaires used to assess the severity of subjective sleepiness (Johns, 1993). Objective sleepiness can be assessed using the Maintenance of Wakefulness Test, the Multiple Latency Test and the Oxford Sleep Resistance Test (Moldofsky, 1992, Arand et al., 2005).

1.6 Treatment of obstructive sleep apnoea

Given that treatment of OSA is not the focus of this thesis, only a brief description of the available treatment options for OSA is presented here.

Both surgical treatment and non-surgical options are available for the management of OSA. Non-surgical options consist of:

- Lifestyle and behaviour modifications such as weight loss and/or change of sleep habits (i.e. avoiding sleeping on one's back);
- mechanical measure of application of positive airway pressure, which can be delivered as continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP); and
- application of oral appliances, such as the mandibular advancement or tongue retaining device (Abad and Guilleminault, 2003).

First line treatment for OSA is CPAP application. Continuous positive airway pressure delivered through a mask, pneumatically splints the upper airway, preventing the airway from collapsing and reduces AHI (Epstein et al., 2009). Utilisation of CPAP is recommended for the treatment of moderate and severe OSA, self-reported sleepiness, the improvement of quality of life, and as an additional therapy to lower blood pressure in hypertensive patients diagnosed with OSA (Epstein et al., 2009, McDaid et al., 2009). In cases of CPAP intolerance by the patient, management with the BiPAP application can be trialled, followed by oral appliances (mandibular prepositional appliances and tongue retaining devices). Behaviour treatment options such as weight loss,

exercise, positional therapy (method used to avoid sleeping on the back, e.g. alarm, use of a tennis ball) and avoidance of alcohol and sedatives before bed time can also be recommended (Epstein et al., 2009). Surgical intervention can be considered if OSA appears to be caused by surgically correctable anatomical abnormalities or may be indicated for patients who are not suitable for CPAP application, or have failed CPAP or BiPAP treatment (Abad and Guilleminault, 2003). A number of surgical procedures are available for the treatment of OSA including: septoplasty, nasal polypectomy, turbinoplasty, tonsillectomy, tracheostomy, uvulopalatopharyngoplasty, genioglossus advancement, mandibular advancement, maxillary advancement, and radiofrequency ablation of the soft palate and the tongue (Sundaram et al., 2005).

Each treatment option should be continuously assessed and outcome measures monitored appropriately. For example, following commencement of CPAP treatment the patient should report a better quality of sleep and consequently an improvement in quality of life. As a recognised chronic disease, patients will require lifelong CPAP treatment for OSA and long term follow-up (Epstein et al., 2009).

1.7 Prevalence of obstructive sleep apnoea

Population-based studies have revealed an unexpectedly high prevalence of OSA in adults (Young et al., 2002a). According to the data from the large and ongoing, population-based Wisconsin Sleep Cohort Study in the United States, the prevalence of diagnosed OSA in the general population (30-60 year olds) was estimated to be 4% in men and 2% in women between 1988 and 1994 (Young et al., 2002a). Moreover, reports from around the world suggest the prevalence of OSA is increasing at an alarming rate (Peppard et al., 2013). A recent study by Peppard et al., (2013) that combined data from the Wisconsin Sleep Cohort Study and the US National Health and Nutrition Health Examination Survey found a significant increase in the prevalence of OSA in the population for the period between 2007 and 2010. According to the study, the current estimated prevalence of moderate to severe OSA in adults between 30 to 70 years of age was 13% in men and 6% in women (Peppard et al., 2013). These authors also estimated that 14% of men and 5% of women have daytime symptoms of sleepiness, which is a

positive indicator of OSA (Peppard et al., 2013). A 2009 study conducted in South Australia, that examined the community prevalence of OSA symptoms and daytime sleepiness reported that 27.8% of the surveyed population (n=835, total 3007 participants) could be classified as being at high risk of OSA using the STOP-BANG measure (Adams et al., 2012).

Although few studies have reported on the prevalence of OSA in surgical patients, several studies have demonstrated that the prevalence of undiagnosed OSA is higher in the surgical population than it is in the general population (Kripke et al., 1997, Finkel et al., 2009, Singh et al., 2013). A historical cohort study conducted by Singh and colleagues (2013) to determine the prevalence of OSA in the general surgical population found that although the proportion of patients in the study with OSA was 13.5%, only 85% of patients were successfully identified as having OSA by an anaesthetist and only 42% of OSA patients were identified by a surgeon (Singh et al., 2013). This study demonstrated that despite the pre-operative patient assessment, anaesthetists and surgeons failed to identify OSA in patients, further highlighting the possibility that OSA can be overlooked by clinicians as a co-morbidity in the peri-operative population (Singh et al., 2013).

A prospective study by Stierer et al., (2010) investigating the prevalence of diagnosed OSA and symptoms of undiagnosed OSA in a cohort of 2139 ambulatory surgical patients, found that 4.8% of patients were at high risk of OSA and that 75% of the patients with a high propensity for OSA were not diagnosed (Stierer et al., 2010). Similar results were demonstrated in a study by Finkel et al., (2009) who conducted a prospective observational study on the prevalence of undiagnosed OSA among surgical patients attending preoperative assessment for elective surgery. Of the 2778 patients who completed the OSA risk questionnaire, 661 (23.7%) were identified as high risk for OSA of which 534 (81%) were not diagnosed with OSA (Finkel et al., 2009). These studies highlight that an alarming proportion of patients with undiagnosed OSA are unaware of their condition and are therefore unable to warn their healthcare providers of their condition during the pre-operative consultation.

1.8 Risk factors for obstructive sleep apnoea

Known risk factors for OSA are obesity, male gender, menopause, older age (>60 years old), genetic predisposition, anatomic abnormalities, nasal congestion at night, cigarette smoking and alcohol intake before bed time (Young et al., 2004). While the physiological mechanisms of OSA remain unclear, the association between these factors and OSA has been reported by numerous studies (Ancoli-Israel et al., 1991, Shelton et al., 1993, Malhotra et al., 2002, Cowan and Livingston, 2012, Peppard et al., 2013). The main risk factors for OSA, including obesity, male gender and advanced age, are briefly discussed in the sections below.

1.8.1 Obesity

The most common contributing factor to the development of OSA is obesity. The body mass index (BMI) is the most common method used to classify obesity and is calculated as one's weight in kilograms divided by the square of one's height in metres (kg/m^2). Table 1.2 provides data on the classification of obesity as defined by the World Health Organisation. According to the World Health Organisation, a BMI greater than $25 \text{ kg}/\text{m}^2$ is considered to be overweight and a BMI of 30 and above is classified as obese (Public Health England 2014).

Table 1.2 The World Health Organisation obesity classifications

Body Mass Index range (kg/m^2)	Classification
≤ 18.5	Underweight
18.5-24.9	Healthy weight
25.0-29.9	Overweight
30.0-34.9	Obesity 1
35.0-39.9	Obesity 2
≥ 40	Obesity 3

Obesity is an extremely prevalent condition reaching epidemic proportions in the general population. Statistics from the United Kingdom presented by the Health and Social Care Information Centre show that there was a marked increase in the proportion of adults that were obese. For example, obesity in men increased from 13% in 1993 to 24% in 2011, and obesity in women increased from 16% to 26% over the same period (Public Health England 2014). The National Health and

Nutrition Examination Survey conducted in the United States found that more than half of the adults in the United States were overweight and 32.2% were obese according to the BMI weight status categories (Ogden et al., 2006).

Obesity is associated with increased prevalence of OSA. A relationship between weight gain and increased severity of OSA (Peppard et al., 2000) was found in a sample of participants from the large population-based Wisconsin Sleep Cohort Study (Young et al., 1993). The continuing 4-year prospective follow-up study, demonstrated that weight gain worsened the severity of OSA while weight loss improved OSA in obese individuals (Peppard et al., 2000). A 10% weight increase predicted an approximately 32% (95% CI, 20%-45%) increase in AHI. Conversely, a 10% weight loss predicted a 26% (95% CI, 18%-34%) decrease in AHI. A 10% weight gain predicted a 6-fold (95% CI, 2.2-17.0) increase in the odds of developing moderate to severe sleep disordered breathing (Peppard et al., 2000). However, the researchers could not address the association between weight loss and reduced OSA severity in normal weight ($BMI < 25 \text{ kg/m}^2$) participants with OSA (Peppard et al., 2000). Similarly, Goudra et al., (2014) reported that 60 out of a total of 101 patients with a BMI of 40-49.9 kg/m^2 had a positive history of OSA (Goudra et al., 2014). The same study showed that the incidence of OSA increased with increasing severity of obesity, where 10 out of 14 patients with a BMI of 50-59.9 kg/m^2 were previously diagnosed with OSA.

Huang et al., (2014), in their retrospective study on the influence of obesity in Chinese patients with OSA, found that the severity of OSA was higher in men, when compared with BMI-matched women (Huang et al., 2014). The AHI was significantly higher in male patients than in female patients in three BMI groups (not overweight, $BMI < 24$; overweight, $BMI 24-27$; and obese, $BMI > 27$). In the non-overweight group AHI was 28 ± 21 per hour for males and 18 ± 17 per hour for females ($P < 0.001$); in the overweight group, AHI was 34 ± 23 per hour for males and 23 ± 20 per hour for females ($P < 0.001$); in the obese group, AHI was 50 ± 29 per hour for males and 27 ± 25 per hour for females ($P < 0.001$). As BMI increased, participants' AHI, arousal index and desaturation index increased, while mean saturation and the lowest saturation index decreased significantly in male patients.

The findings of this study confirmed that increases in BMI contribute to the severity of OSA (Huang et al., 2014).

Obesity is associated with a range of physical changes that positively correlate with OSA occurrence. There are several mechanisms that may explain how obesity has an effect on the severity of OSA. First, the increased deposition of fat that accumulates around the pharyngeal lateral airway counteracts with the maintenance of the airway patency and can contribute to airway obstruction during sleep. During sleep, the pharyngeal fat padding that forms around the upper airway in obese patients collapses onto the airway, leading to restricted breathing (Horner et al., 1989, Hoffstein and Mateika, 1992). Fat deposition around the neck, measured as a neck circumference, is an important and independent predictor for the severity of OSA (Horner et al., 1989, Hoffstein and Mateika, 1992). A comparative computed tomography scan study of the upper airways between patients with mild OSA and BMI-matched habitual snorers demonstrated that the pharyngeal fat pad area was significantly larger in the OSA group, than in the snorers group ($p=0.002$) (Pahkala et al., 2014). A subsequent one-year follow-up study, involving a weight loss program, demonstrated a significant reduction in central obesity and the amount of fat tissue in the pharynx in OSA patients. The authors also reported a reduction in AHI, and concluded that the weight loss reduced the excessive oropharyngeal fat tissue in overweight patients with OSA and consequently improved their OSA (Pahkala et al., 2014). Therefore, it seems that weight loss by obese individuals might not only improve OSA severity, but may also potentially prevent its occurrence. Furthermore, upper airway collapsibility is more likely in obese compared to non-obese patients (Schwartz et al., 1991). Obesity, and especially central obesity, are also associated with reductions in lung volume (Sharp et al., 1964). Similarly, obesity imposes a mechanical load on the upper airway and respiratory system, narrowing the upper airway, predisposing the airway to collapse, which results in the obstruction of airflow during sleep (Schwartz et al., 2008).

Independently, obesity is associated with co-morbidities such as hypertension, type 2 diabetes, cardiovascular disease (Hirani et al., 2008) and OSA (Rice et al., 2015). Obesity in surgical patients increases risk of complications in the peri-

operative period (Glance et al., 2010). Ultimately, the association between obesity with other co-morbidities places patients with OSA into the high-risk group for complications when they present for a treatment to a health care facility.

1.8.2 Age

Population-based studies have demonstrated an increase in OSA prevalence with advancing age (Ancoli-Israel et al., 1991, Young et al., 2002b, Lee et al., 2014). Between 1981-1985, Ancoli-Israel et al., (1991) conducted a large, population-based survey of sleep disordered breathing (SDB) in older adults. The researchers examined objective and subjective information on randomly selected elderly people, 65 years or older, in the city of San Diego, California. A sample of 427 people agreed to undertake sleep measurements and a post-sleep questionnaire. The combined mean age of men and women was 72.5 years (SD=6.1). The study authors reported that 24% of the total population under investigation had an apnoea index (AI) >5 and 62% had a RDI of >10. Women showed significantly less sleep disordered breathing than men, with an AI >5 in 20% of the sample, compared to 28% of men ($p<0.05$). Mild sleep disordered breathing (AI >10) was reported in 10% of participants; AI >20 was reported in 4%; and AI >40 was reported in 1%. The authors reported a high number of hypopnoeas, wherein 44% of the sample had an RDI >20 and 18% of the sample population had an RDI >50 (Ancoli-Israel et al., 1991).

Of notable significance however, are the findings from a follow-up study on the same population and published in 2001 by the same authors (18 years from commencement of the previous study), who concluded that the changes in RDI were associated with changes in BMI, and were independent of age (RDI: $t_{201}=-0.91$, $P=0.3651$), (Ancoli-Israel et al., 2001). Regression analyses showed that variables such as BMI at the initial visit ($P=0.001$), change in BMI ($P=0.02$), and consistent self-reports of high blood pressure ($P=0.005$) were significantly associated with changes in RDI. The study results suggest that RDI remains stable if BMI continues to be stable (Ancoli-Israel et al., 2001). Despite the findings from the follow-up study by Ancoli-Israel et al., (2001), age is still considered a risk factor for SDB.

The Sleep Heart Health Study, which included 5615 men and women aged between 39-99 years, investigated the association between gender, age, race, snoring and obesity with SDB in community dwelling adults (Young et al., 2002b). In the study sample, 53% of participants were women (mean age: 63.5 years, $SD \pm 10.7$ years). The authors of the study presented data from the sample in three categories of AHI (<5, 5-15, and >15) and defined a SDB as an AHI of 15 or greater. The authors reported a small increase in SDB prevalence with increasing 10-year age groups. When modeled with age as a continuous variable, a 10-year age increment was associated with an increase in the odds of having an AHI of 15 by 24%. In their study, prevalence of SDB rates in the 39-49 year old age group for an AHI 5-14 was 19%, and an AHI >15 was 10%. In the 60-69 age group, prevalence of SDB with an AHI of 5-14 was 32%, and with an AHI of >15 was 19%. The next age group of 70-79 year olds demonstrated 33% for an AHI of 5-14, and 21% for an AHI >15. The study revealed a small increase of AHI in people over 60 years of age. The same authors also reported that prevalence of SDB began to level off after the age of 60 and concluded that an age related increase in SDB occurs before the age of 65 years (Young et al., 2002b).

In developed countries there is a clear demographic pattern of increasing longevity. As the number of older people increases, there is likely to be an increased prevalence of OSA, including undiagnosed OSA, in the general population. It is critical, therefore, to establish a knowledge base around delivery of safe care for patients with OSA.

1.8.3 Gender

Male gender is a recognised risk factor for OSA (Young et al., 1993), with OSA being more common in men than in women (see Section 1.7). According to the Sleep Heart Health Study, moderate OSA (defined as AHI of 15 or greater) is approximately twice as prevalent in men than in women (Young et al., 2002b). Using multiple logistic regression models with the cumulative addition of variables such as gender, age and race, the study found that men had 2.7 times the odds of having moderate OSA than women (Young et al., 2002b).

There are multiple hypotheses as to why male gender is a risk factor for OSA. One explanation for men's increased risk for OSA is the different anatomical fat

tissue distribution around the airway that is found in men compared to women (Whittle et al., 1999). In their study, Whittle et al., (1999) used magnetic resonance imaging to measure fat and tissue volumes in the neck of ten non-obese men and women, matched by age and BMI, and without symptoms of SDB (Whittle et al., 1999). According to the study results, the total neck soft tissue volume was greater in men (1295 cm³) than in women (928 cm³, p=0.0002) although the actual volume of fat was similar in both genders (291 cm³ in men versus 273 cm³ in women, p=0.6). Fat in the neck soft tissue was compared with the percentage of fat in the whole body. Fat distribution in the neck was analysed further and two regions were identified where men had a greater absolute volume of fat than women: anterior and posterior segments inside the mandible at the palatal level. The authors concluded that the increased fat loading around the airway in men may be a contributing factor for the increased prevalence of SDB development in men (Whittle et al., 1999).

In an earlier study, Brooks and Strohl (1992) investigated the association between gender and OSA, and studied the anatomy and physiology of the upper airway of normal men (n=98) and women (n=124). The authors investigated the mechanical properties of the pharynx of men and women and discovered that men have a larger pharynx and different pharyngeal mechanics than women (Brooks and Strohl, 1992). It was concluded that gender was the most important independent factor contributing to pharyngeal size and speculated that the size of the larynx predisposed men to OSA (Brooks and Strohl, 1992). Therefore, although it is not clear why men are more likely to develop SDB, multiple factors may play a role in the male gender's predisposition to OSA.

1.9 Procedural sedation and analgesia

Procedural sedation administration is often required to overcome the discomfort associated with painful or uncomfortable medical procedures. Carefully titrated drugs can be tailored to a specific procedure to provide a desired level of sedation. Examples of procedures where sedation is routinely administered include upper endoscopy, colonoscopy (Triantafillidis et al., 2013), bronchoscopy (Ni et al., 2010), cardiac studies (e.g. catheter ablation, cardioversion, coronary artery angioplasty) (Salukhe et al., 2012, Fazelifar et al., 2013, Furniss and Sneyd,

2015), radiological investigations (e.g. cerebral angiogram; insertion of various intravascular devices) (Skehan et al., 2000), bone marrow biopsy (Zahid, 2015), dental procedures (Boynes et al., 2010, Sago et al., 2015) urological procedures (Kim et al., 2014, Tsuji et al., 2014, Krocak et al., 2016) and plastic procedures (Cillo and Finn, 2005). Sedation can also be administered for a vast range of other therapeutic or diagnostic medical procedures where severe discomfort is anticipated or where a patient's anxiety is an obstacle to undertaking the procedure (e.g. magnetic resonance imaging) (Martin and Lennox, 2003).

Generally speaking, any medical intervention is, at a minimum, an unpleasant experience for the patient. Anxiety and 'fear of the unknown' are common reactions prior to any medical examination or treatment and PSA is often considered to avoid causing physical and psychological trauma to the patient and to facilitate a patient's comfort and cooperation during the procedure. According to the Australian New Zealand College of Anaesthetists (ANZCA) Guidelines to Sedation and Analgesia for Diagnostic and Interventional Medical, Dental or Surgical procedures, the definition of PSA implies that "the patient is in a state of drug induced tolerance of an uncomfortable or painful procedure. Lack of memory for distressing events and/or analgesia are desired outcomes, but lack of response to painful stimulations is not assured" (ANZCA Guidelines, 2014, p.1).

As with all interventions, side effects associated with the administration of drugs to achieve sedation and analgesia must be considered. Consequently, PSA involves fine-tuning the balance between the patient's level of comfort and any unwanted side effects associated with the drug's administration. In general terms, sedation can be described as occurring on a continuum from an awake and alert state through to general anaesthesia (ANZCA Guidelines, 2014). There are always risks associated with PSA as a patient transition from full alertness through various depths of sedation to general anaesthesia. Depending on the physiological processes that are taking place such as consciousness, maintenance of the airway, spontaneous ventilation and cardiovascular function, sedation can be described as conscious sedation, deep sedation or general anaesthesia (ANZCA Guidelines, 2014). Definitions describing conscious sedation, deep sedation and general anaesthesia are outlined below.

Conscious sedation can be defined as a drug induced depression of consciousness wherein the patient purposefully responds to instructions or light tactile stimulation. In this state, the patient can control and maintain their airway, spontaneous ventilation and cardiovascular function (ANZCA Guidelines, 2014). The patient can be described as relaxed, cooperative and able to respond to commands. If the patient drifts into sleep, they can be easily roused. Deep sedation is a medically controlled depressed state of consciousness. The patient is unconscious and does not purposefully respond to verbal commands, tactile or painful stimulation. This level of sedation is associated with partial or complete loss of airway reflexes, inadequate spontaneous ventilation and impaired cardiovascular function (ANZCA Guidelines, 2014). Deep sedation predisposes the patient to similar risks as general anaesthesia. General anaesthesia is a drug induced state of reversible unconsciousness (hypnosis) and is characterised by unresponsiveness to verbal or tactile stimulation. Loss of consciousness results in amnesia, a suppression of antegrade memory and unawareness of the environment and ultimately of surgical stimulation (Stuth et al., 2012). General anaesthesia is associated with the loss of protective airway reflexes, the depression of respiration and cardiovascular function (ANZCA Guidelines, 2014).

A variety of intravenous drugs are available to achieve PSA. Alone or in combination, hypnotic sedative agents (e.g. propofol), benzodiazepines (e.g. midazolam) and opioids (e.g. fentanyl) are widely used by various medical specialists to form a sedation regimen (Vargo et al., 2012, Fazelifar et al., 2013, Thomas et al., 2014, Ferreira and Cravo, 2015). Depending on the drug, the dosage, the administration of other medications and the patient's current (medical) state, the drugs elicit different effects via action on the central nervous system and therefore produce different levels of sedation. Detailed information on the most commonly used drugs such as propofol, fentanyl and midazolam is presented in the sections below.

1.9.1 Propofol

Propofol (2,6-diisopropylphenol) is a short acting general anaesthetic agent. Propofol produces its sedative/anaesthetic effect via binding to, and activating, gamma-aminobutyric acid (GABA) receptors (MIMS Australia 2016). Depending

on the dose and length of administration, the drug has a rapid onset of action of approximately 30 seconds, and also a rapid offset of action, allowing rapid awakening (AMH 2016). The duration of action of a single bolus of propofol is 5-10 minutes. The elimination phase of propofol is 30-60 minutes (AMH 2016). Propofol is indicated for induction and maintenance of general anaesthesia, sedation for medical procedures, and for the sedation of ventilated patients (AMH 2016). The drug does not possess any analgesic properties, therefore analgesics need to be considered to control pain (AMH 2016, MIMS Australia 2016). Propofol possesses antiemetic, anxiolytic, antipruritic, bronchodilatory and anti-epileptic properties (Lundstrom et al., 2010).

Propofol can be administered intravenously only. The drug can be given as a single bolus or as a continuous infusion. Depending on the dose administered and the patient's factors, the therapeutic spectrum of propofol varies from mild sedation through to general anaesthesia (Stuth et al., 2012). For example, a low dose of propofol will have a sedative effect while a high dose can induce unconsciousness (Stuth et al., 2012). When used for sedation for medical or surgical procedures, and depending on the depth of sedation required, the individualised dose of propofol can be given as a bolus. Propofol exhibits significant variability in dosage requirements. Patient factors that may contribute to this variability include age, the current clinical status of the patient (e.g. septic shock, hypovolaemia) and co-administration of central nervous system depressants (e.g. opioids). Therefore, the dose of propofol needs to be titrated in small increments to avoid unwanted loss of consciousness (AMH 2016, MIMS Australia 2016). Due to the short elimination half-life of propofol, repeated boluses can be administered during the course of sedation.

For the maintenance of sedation, propofol infusion (1.5-3 mg/per kg of body weight per hour) can be titrated to the desired level of sedation. An extra bolus of 10-20 mg of propofol can be added if a deeper level of sedation is required (AMH 2016). For induction of general anaesthesia, a single bolus (1.5-2.5 mg/per kg of body weight) of propofol can be administered to rapidly induce unconsciousness (AMH 2016). However, elderly patients are more sensitive to the anaesthetic effects of propofol, as well as its side effects (Phillips et al., 2015). A recent study

by Phillips et al., (2015) demonstrated that an increased dose of propofol administered to patients over 65 years of age was associated with increased post-induction hypotension. Therefore, extra care and smaller doses of propofol need to be considered when administering propofol to geriatric patients. The advantages of propofol including titratable depth of sedation, rapid onset and rapid offset of action, quick recovery from sedation and anti-emetic property of the drug, make it an ideal sedation drug for ambulatory procedures.

Common (>1%) side effects associated with propofol are pain at the injection site, bradycardia, hypotension, apnoea, flushed skin or rash, cough, and excitation at induction (tremors, twitches, hiccups) (AMH 2016). A reduced rate of injection is recommended to minimise cardiovascular depression during propofol administration (AMH 2016). Among the less frequent (0.1-1%) adverse effects of propofol are arrhythmias, thrombosis and phlebitis at the injection site (AMH 2016). The incidence of cardiac and respiratory depression increases with increasing doses of propofol (Stuth et al., 2012).

Obstructive sleep apnoea is emerging as a common phenomenon in the population presenting for procedural sedation. The major concern in patients with OSA is the risk of airway obstruction during propofol sedation. In a recently published study (Koo et al., 2015), researchers investigated the relationship between propofol concentration, sedation and OSA. In this study, 25 patients were sedated with a propofol target-controlled method of infusion in order to perform DISE and assess the cause of apnoea and snoring. All 25 patients had subjective symptoms such as snoring, daytime sleepiness, morning headaches, sleep disturbance, fatigue and an AHI >5 recorded during attendance at an overnight PSG. The authors reported that increased propofol concentration correlated with depth of sedation and severity of airway obstruction. The concentration of propofol for each sedation and an airway obstruction score in patients with OSA was obtained, and it was found that AHI was a significant covariate in the relationship between propofol and severe airway obstruction. The authors concluded that the difference between the predicted values for each level of sedation was small, and the values for each probability curve of sedation were relatively high. The model parameters for sedation confirm a narrow therapeutic window of propofol, proving that it is easy

to induce unwanted deep sedation or provide inadequate sedation (Koo et al., 2015). Moreover, given propofol's narrow margin of safety, unintended deep sedation with unconsciousness or general anaesthesia can be inadvertently induced, resulting in the loss of airway patency.

In their study on nine healthy volunteers, Hillman and co-workers (2009) evaluated changes in upper airway collapsibility during propofol induction and upper airway muscle activity. The focus of the study was to determine the association between loss of consciousness during slow propofol injection and changes in upper airway collapsibility. The study results showed that loss of consciousness occurred even with low doses of propofol administration (Hillman et al., 2009). Genioglossus electromyographic activity was measured and decreased significantly to a minimal value at, or approaching, loss of consciousness. The authors concluded that propofol anaesthesia is associated with an increase in upper airway collapsibility (Hillman et al., 2009). There is no reversal agent for propofol; remediation of unintended deep sedation or general anaesthesia requires maintenance of the airway and assisted ventilation until the drug has been metabolised and the patient returns to consciousness.

The outlined disadvantages of propofol, including the absence of analgesic effect, its narrow therapeutic index, cardiac and respiratory depression, the widely variable effective dose between individuals, and the absence of a reversal agent need to be considered when propofol is used to facilitate sedation.

1.9.2 Midazolam

Midazolam is a 1,4-benzodiazepine derivative from the imidazobenzodiazepine group (MIMS Australia 2016). Midazolam is a short-acting central nervous system depressant. By interacting with GABA receptors, midazolam depresses the central nervous system, resulting in sedation, anxiolysis, hypnosis, antegrade amnesia and anaesthesia (Gamble et al., 1981, Kanto and Allonen, 1983, Reves et al., 1985, Khanderia and Pandit, 1987). Intravenously administered midazolam has a rapid onset of action (2-5 minutes). In normal subjects, depending on the dose administered and renal function, the mean elimination half-life is 1.4-2.4 hours (MIMS Australia 2016). In elderly adults (over 60 years of age), the

elimination half-life might be prolonged by up to four times (MIMS Australia 2016).

Early studies examining the effects of midazolam demonstrated that even small doses of the drug can produce an anxiolytic effect (Pieri, 1983), while higher doses can produce amnesic effects (Dundee and Wilson, 1980, Miller et al., 1989). The desired sedative end point, as indicated by a slurred speech, is attained within 2.8-4.8 minutes, with 2.5 mg administered intravenously as a bolus (Pieri, 1983). Midazolam is indicated for premedication, conscious sedation, sedation of mechanically ventilated patients and as a co-induction agent for general anaesthesia (AMH 2016). It is strongly recommended that midazolam is administered slowly while observing the patient's response. The sedative effect should be evaluated two minutes after midazolam administration (Oikkola and Ahonen, 2008, AMH 2016, MIMS Australia 2016). Repetitive boluses of 1 mg of midazolam can be repeated to maintain the state of sedation. In higher doses (e.g. 10-15 mg), midazolam can be used to induce general anaesthesia (MIMS Australia 2016).

The individual response to midazolam can vary, and will depend on the patient's age and clinical presentation, and the use of other medications (e.g. other central nervous system depressants). Reduced doses of midazolam should be considered for patients with acute illness (e.g. fluid or electrolyte imbalance), renal impairment, hepatic impairment, congestive heart failure and obesity. Patients with chronic obstructive pulmonary disease are very sensitive to the respiratory depressant effect of midazolam, and are therefore predisposed to apnoea (AMH 2016, MIMS Australia 2016). Extra care needs to be taken when administering midazolam to the elderly as they are under a higher risk of over-sedation, respiratory depression, confusion and falls (AMH 2016). Lower doses and slower administration rates are recommended for the elderly (AMH 2016, MIMS Australia 2016).

An increased sedative effect of intravenously administered midazolam may result from co-administration with anaesthetic and analgesic agents, antidepressants, sleep inducing drugs, antipsychotics and sedative antihistamines (MIMS Australia 2016). Careful titration and a reduced dose of midazolam, as well as vigilant

patient assessment during sedation needs to be considered when midazolam is co-administered with other central nervous system depressants (AMH 2016, MIMS Australia 2016). When midazolam is used in combination with opioid analgesics (e.g. fentanyl) it is recommended to reduce the dose of both agents, as both midazolam and opioids enhance the effects on sedation, respiration and haemodynamics (MIMS Australia 2016).

Midazolam can also be administered orally, intramuscularly or as intranasal drops (commonly used with paediatric patients). Depending on the route of administration, the dose, and the administration of other medications, midazolam can produce different effects on the central nervous system, and consequently different levels of sedation (Oikkola and Ahonen, 2008, Stuth et al., 2012). When unexpected central nervous system depression is observed, intravenously administered flumazenil can reverse the action of midazolam. Potential adverse effects following intravenously administered midazolam include respiratory depression, apnoea, cardiovascular depression (hypotension), post-operative sedation, decreased alertness, headaches, confusion, hallucinations, hyperactivity and delirium (AMH 2016, MIMS Australia 2016).

Midazolam is commonly used during diagnostic and short medical procedures, and either alone or in combination with other drugs, forms a sedation regimen. The anxiolytic effect alone makes midazolam a drug of choice when sedation is required. As an anxiolytic drug, midazolam is also often used as a singular drug for non-invasive medical examinations (e.g. magnetic resonance imaging) when relaxation is required. Similarly, the anti-anxiety properties of midazolam makes this drug also very popular as an adjuvant to propofol (Newman and Reves, 1993). Midazolam does not produce an analgesic effect, therefore, a drug with analgesic properties needs to be added in cases where pain or discomfort are anticipated.

In summary, midazolam is a commonly used drug for sedation; in low doses midazolam produces anxiolysis, in moderate doses it produces sedation and amnesia, and in high doses it produces general anaesthesia. The wide therapeutic index of midazolam, and the existence of the antagonist drug flumazenil, makes this drug a reasonably safe option when conscious sedation is required.

1.9.3 Fentanyl

Fentanyl is a synthetic opioid analgesic with a rapid onset of action. Fentanyl has a strong affinity to the opioid μ -receptors in the peripheral and central nervous system. By activating μ -receptors in the central nervous system, fentanyl provides excellent analgesia. An intravenously administered bolus dose of fentanyl of up to 100 micrograms for adult patients will reach peak analgesic effect within several minutes. The duration of action of fentanyl is 30-60 minutes; the half-life is 2-7 hours (MIMS Australia 2016). A potent analgesic, fentanyl is indicated as a pre-medication, adjuvant to induction of general anaesthesia, as pain relief during the peri-operative period and for breakthrough pain in cancer patients (AMH 2016, MIMS Australia 2016). Fentanyl is frequently used as an analgesic agent to supplement propofol or midazolam when intravenous sedation administration is required. The drug can be administered intravenously, intramuscularly, subcutaneously and as intranasal drops (commonly used with paediatric patients).

Along with the desired therapeutic effect, fentanyl administration can cause unwanted respiratory adverse effects such as respiratory depression or apnoea (AMH 2016, MIMS Australia 2016). In the case of undesired adverse events, the opioid receptor antagonist naloxone is available to reverse the action of fentanyl (AMH 2016, MIMS Australia 2016). Central nervous system depressants such as anaesthetics and benzodiazepines might have an additive effect on fentanyl and may enhance its action. Therefore, when other central nervous system depressants are used, the dose of fentanyl may need to be reduced (AMH 2016, MIMS Australia 2016). Similarly, the dose of any other central nervous system depressants, when used following fentanyl administration, needs careful monitoring and may need to be reduced following fentanyl administration (AMH 2016, MIMS Australia 2016).

Cardiovascular adverse effects such as hypotension and bradycardia are possible with fentanyl administration. Patients receiving calcium channel blockers in combination with beta-adrenergic blockers might develop severe hypotension following fentanyl administration. At the same time, bradycardic and hypovolemic patients are at higher risk of developing hypotension (MIMS Australia 2016). Reduced doses of fentanyl should be considered to avoid

undesired effects of the drug (AMH 2016, MIMS Australia 2016). The bolus dose of fentanyl needs to be carefully selected and will depend on the age, the clinical presentation of the patient and the co-administration of other drugs. Extra care needs to be taken when fentanyl is administered to elderly and debilitated patients. As the elderly are more sensitive to opioids (MIMS Australia 2016 , AMH 2016) reduced doses of fentanyl should be administered, or the drug should not be used at all, to avoid side effects associated with the drug.

In summary, the rapid onset of action and the reasonably prolonged analgesic effect of fentanyl has gained the drug popularity as an analgesic supplement when pain relief is required during stimulating medical procedures. However, the adverse events associated with administration of the drug should not be overlooked and extra care should be taken when fentanyl is administered to elderly and fragile patients.

1.10 Safety of procedural sedation administration

As outlined in the preceding sections, depending on the anticipated level of discomfort during a procedure and patients' specific needs, agents with sedative or hypnotic properties, such as midazolam or propofol are commonly used for procedural sedation. However, there is a risk of unintended deep (unconscious) sedation or even general anaesthesia associated with PSA. For example, propofol has a very narrow therapeutic margin and the risk of losing consciousness is high. The loss of consciousness in the Hillman et al., (2009) study was associated with an upper airway collapse during propofol anaesthesia; therefore, it is reasonable to hypothesise that a similar process involving loss of the airway may occur following fentanyl or midazolam administration. While it appears that no research on fentanyl and midazolam has been conducted to confirm that the airway collapse when those drugs (alone or in combination) are administered, it is quite possible, that the synergetic effects of the drugs may unintentionally lead to a state of deep sedation or general anaesthesia. Therefore, the unexpected loss of consciousness can place a patient in a dangerous state that requires immediate intervention.

Studies have shown that midazolam decreases spontaneous minute ventilation (Reves et al., 1985, Bailey et al., 1990), while fentanyl alone produces significant

hypoxemia and a decrease in ventilatory response to carbon dioxide (Bailey et al., 1990). Furthermore, research has demonstrated that the combination of fentanyl and midazolam significantly increase the incidence of hypoxemia and apnoea (Bailey et al., 1990, Stuth et al., 2012). A synergistic hypotension effect is also common when benzodiazepines and opioids are used together (Newman and Reves, 1993). Consequently, a patient's safety during sedation administration is in the hands of the healthcare provider administering sedation. Clinicians administering procedural sedation to their patients are therefore expected to have the necessary skills and knowledge in the management of the airway of the unconscious and/or haemodynamically unstable patient. Considering the potential complications that may occur following administration of fentanyl, midazolam and particularly propofol, by non-anaesthetists, the question of safety of PSA to the patient with OSA, diagnosed or undiagnosed, remains a valid and unresolved issue.

1.11 Why a systematic review is needed

As indicated in Section 1.1, a recent systematic review was published on the topic of interest (Gaddam et al., 2015). Gaddam and colleagues (2015) reported on the incidence of respiratory and cardiac complications during GI endoscopies with PSA in patients with diagnosed OSA and at high risk for OSA. Only studies with confirmed OSA by PSG diagnosis were considered in this review.

Worldwide, thousands of medical procedures under sedation occur daily. Given the burgeoning interest and controversial opinions in the medical literature surrounding the safety of anaesthetic, opioid and benzodiazepine administration, it is important that clinicians understand the risks associated with these drugs when administering procedural sedation to the OSA population. This systematic review examines the incidence of cardiopulmonary outcomes associated with the administration of propofol, fentanyl and midazolam to patients with confirmed OSA. The review also identifies gaps in the evidence across the included studies and provides a basis for understanding future research needs within this field.

Despite the small number of studies located and the limited number of patients involved, this systematic review provided the opportunity to collectively examine

the available studies on this topic in order to improve our understanding of the safety of sedation administration to patients with confirmed OSA. The results of this review will potentially allow for the promotion of safe practice when caring for OSA patients during the peri-operative period (Gagolkina et al., 2014, *a priori* protocol, Appendix 1).

1.12 Review question and objective

The purpose of this systematic review was to synthesise the best available evidence concerning the cardiovascular and respiratory adverse events associated with PSA in patients with OSA.

To achieve this objective, the review question was:

- What is the incidence of peri-operative cardiopulmonary adverse events associated with PSA in patients with OSA?

1.13 Inclusion criteria

Population of interest

This review considered studies of patients, 18 years and older, formally diagnosed with OSA (as determined by a formal sleep study, e.g. PSG) who underwent a diagnostic or therapeutic procedure with intravenous PSA. Studies that included patients at high risk for OSA or did not define the methods used to diagnose OSA (e.g. PSG results) were excluded from this review.

Intervention

Studies that evaluated (1) midazolam or fentanyl alone or in combination; or (2) propofol, with or without supplementary drugs including midazolam and fentanyl administered to facilitate PSA for OSA patients. Studies on OSA patients receiving sedation for drug induced sleep studies to examine upper airways, or receiving general anaesthesia were excluded from this review.

Outcomes

The outcomes of interest for this review were cardiovascular and respiratory (cardiopulmonary) adverse events in patients diagnosed with OSA receiving PSA for any medical diagnostic or therapeutic procedure. The studies that reported any adverse events that occurred in OSA patients following administration of drugs

fentanyl, midazolam, propofol (administered alone or in combination) were included. This review considered studies that included the outcome measures (adverse events) as listed below.

Cardiovascular events:

- hypo/hypertension (20% or greater decrease (hypotension) or increase (hypertension) in the pre-procedural blood pressure value or, any single systolic blood pressure reading below 80 mmHg or above 160 mmHg)
- significant arrhythmias (e.g. AV heart block, ventricular tachycardia, atrial fibrillation)
- brady/tachycardia (e.g. ≤ 50 beats per minute, or ≥ 120 beats per minute)
- chest pain
- cardiac arrest
- heart failure

Respiratory events:

- loss of airway patency
- hypoventilation (e.g. respiratory rate ≤ 8 breaths per minute)
- oxygen desaturation (e.g. saturation of oxygen $\leq 92\%$).
- laryngospasm
- bronchospasm
- aspiration

Mortality and morbidity

Studies were excluded if it was not clear, whether the events occurred during sedation or during general anaesthesia administration.

Types of studies

This review considered randomised and non-randomised controlled trials and observational analytic study designs, including prospective and retrospective cohort studies and case control studies for inclusion. Case series were excluded from this review.

There were two different study designs that were considered *a priori* for inclusion (Gagolkina et al., 2014, *a priori* protocol, Appendix 1): (1) studies on an OSA

sample that evaluated the adverse events rates attributable to the different drugs used for PSA: fentanyl, midazolam and/or propofol and (2) studies that compared the OSA population of interest with the non-OSA population, where the effects of the drugs fentanyl, midazolam or propofol administered to the patients were reported. Randomised controlled trials and non-randomised controlled trials would be an applicable study design to compare the effects of different drugs on OSA patients (design 1 above). Observational prospective and retrospective analytic studies would be an appropriate and a practical study method for the assessment of the outcomes of interest in two different population groups (design 2 above).

2. Review Methods

Chapter 2 outlines the systematic review methods, including detailed reporting of the search strategy and the approach taken to the critical appraisal, data extraction and data synthesis of the included studies.

2.1 Search Strategy

Prior to the development of the *a priori* protocol for the systematic review (Gagolkina et al., 2014, Appendix 1) presented in this thesis, an initial search of the *Joanna Briggs Institute Database of Systematic Reviews and Implementation Reports*, and the *Cochrane Database of Systematic Reviews* was conducted to determine if a systematic review on a similar topic had been conducted. An additional search using relevant keywords was undertaken in both CINAHL and MEDLINE in the second half of 2013 to further locate systematic reviews related to the review objective. The latter search uncovered one systematic review (Ankichev et al., 2011) and one meta-analysis (Kaw et al., 2012) that examined the association between sedation/anaesthesia and OSA. Both research syntheses (Ankichev et al., 2011, Kaw et al., 2012) included patients with OSA who had received general anaesthesia for surgical procedures such as orthopaedic, general surgical abdominal, gynaecological, bariatric, neurosurgical, vascular, thoracic, and otolaryngology (see Section 1.1). No other systematic reviews evaluating the effects of PSA in adult patients formally diagnosed with OSA who had undergone therapeutic or diagnostic procedures were found. However, since the completion of the protocol for the current systematic review and during the conduct of the review itself, one systematic review related to the topic of interest was identified. Gaddam and colleagues (2015) published a systematic review with meta-analysis that reported on the incidence of post-procedure complications in patients diagnosed with, or at high risk of OSA, undergoing GI endoscopy procedures (see Section 1.1).

A three-step search strategy was utilised to locate studies for this systematic review. An initial limited search of MEDLINE and CINAHL was undertaken using the terms: ‘obstructive sleep apnoea’, ‘sleep apnoea’, ‘sleep disordered

breathing'; 'sedation', 'anaesthesia and analgesia'; 'fentanyl', 'midazolam', 'propofol'; 'upper airway', 'upper airway obstruction'; and 'safety', 'complication(s)'. Relevant papers from this initial search were closely reviewed to further identify any relevant terms for the second search strategy to be conducted in each included database.

Initially, the aid of an experienced librarian (MB, Acknowledgements) was sought to assist with developing the second electronic search strategy. The concepts for the search, including appropriate search terms, were developed iteratively. Two main concepts 'sleep apnoea' and 'sedation' were combined in the search strategy for each database. The first concept, 'sleep apnoea', and terms describing the condition, were carefully explored in each database, as different terms have been used in the past within the medical literature to describe what is now called 'obstructive sleep apnoea' (see Table 2.1). The second concept, 'sedation', incorporated terms that related to both: (1) 'sedation' or 'anaesthesia' facilitation, and (2) administration of the drugs fentanyl, midazolam, propofol (see Table 2.1).

Table 2.1 Review concepts with search terms

Concept	Search Terms
Sleep Apnoea	Sleep apnoea syndrome, sleep apnea, sleep hypopnoea, OSA, OSAH, OSAHS, apnoea hypopnoea syndrome, apnoea hypopnoea syndrome, sleep disordered breathing, hypersomnia with periodic respiration, upper airway resistance, upper airway obstruction, nocturnal apnoea
Sedation	Short acting anaesthesia, sedation, conscious sedation, procedural sedation, neurolept sedation, anaesthesia or analgesia, anaesthetic, monitored anaesthesia care, fentanyl, midazolam, propofol

OSA = obstructive sleep apnoea; OSAH = obstructive sleep apnoea hypopnea; OSAHS = obstructive sleep apnoea hypopnoea syndrome.

The search strategy was adapted for each of the databases to maximise the retrieval of relevant publications. A set of appropriate medical subject heading terms (CINAHL, MEDLINE) and Emtree terms (EMBASE) were used to

increase the sensitivity of the search strategy.

Particular attention was paid to the spelling of the terms ‘apnoea’ and ‘anaesthesia/anaesthetic’ when the search strategy was developed. The search of each database using only English or only American spelling resulted in a vast difference of citations returned from each database. The optimal number of results occurred when both English and American terms were included in the search strategy. Similarly, plural and singular forms of the terms were carefully tested, and surprisingly revealed a big difference in the results returned from the databases. Hence, a plural form of the search terms were used in the database searches where applicable. The search for studies for inclusion in this review was limited to studies published in the English language only.

Terms such as ‘sleep apnoea syndrome’, ‘sleep hypopnoea’, ‘apnoea hypopnoea syndrome’, ‘sleep disordered breathing’, ‘hypersomnia with periodic respiration’, ‘upper airway resistance’, ‘upper airway obstruction’, and ‘nocturnal apnoea, as well as abbreviations such as ‘OSA’ (obstructive sleep apnoea), ‘OSAH’ (obstructive sleep apnoea hypopnoea), and ‘OSAHS’ (obstructive sleep apnoea hypopnoea syndrome) were commonly used in the historic articles to describe the medical condition. Time was spent testing the terms in each database in order to develop the best direction for the search strategy. Finally, the iterative approach in one search string combined with the Boolean operator “OR” promoted the maximum number of hits relevant to each of the domains and their representation in the literature.

Names of the drugs fentanyl, midazolam, and propofol were concurrently extensively searched in main databases for other terms and chemical formulas when the search strategy was developed. Fewer hits were received when terms other than midazolam, fentanyl or propofol were used in the search. Nevertheless, all possible terms for the drugs of interest were used in the search strategy.

During the testing of the search terms, the concepts ‘sleep apnoea’ and ‘sedation’ were tested separately and then combined via Boolean operator “AND” with the terms ‘upper airway’, ‘upper airway obstruction’, ‘safety’, ‘complication(s)’, ‘morbidity’, ‘mortality’, ‘adverse events’, ‘postoperative complications’ to assess

the number of recalls from the database. The relevant citations were lost during this search; therefore this line of search was dismissed. Studies on animals were manually removed during screening of the titles and the abstracts. They were not included in the list of the excluded studies for this review.

Although descriptions of the disorder began appearing in the medical literature in the 1950s and 1960s (Bickelmann et al., 1956, Drachman and Gumnit, 1962, Jung and Kuhlo, 1965, Gastaut et al., 1966), it took some years for OSA to be identified as a medical condition. Essentially, it was not until the mid-1960s that OSA began to be recognised more widely by the medical profession. The search strategy was therefore designed to locate studies published from 1965 onwards, as it is very likely that searches from that year would capture the relevant literature in the modern medical literature databases.

The initial search was completed on 30 March 2014. The search of major databases continued to run on a monthly basis, and the final search was completed on 15 May 2015. The second stage of the search, using identified keywords and index terms in both English (UK) and American spelling, was undertaken in the databases outlined in Table 2.2 below.

The search for grey literature was completed on 30 March 2014. Grey literature was identified by searching the following websites: ProQuest Dissertations and Theses, Current Controlled Trials (ClinicalTrials.gov), and the Australian New Zealand Clinical Trials Registry (anzctr.org.au) for conference abstracts, dissertations and non-published research findings (Table 2.2). Only the key concepts and terms such as sleep apnoea syndrome, sleep apnoea, obstructive sleep apnoea, sedation, fentanyl, midazolam, propofol, safety, complications were used in the search of unpublished studies in the ProQuest Dissertations and Theses, Current Controlled Trials (ClinicalTrials.gov), and the Australian New Zealand Clinical Trials Registry (anzctr.org.au).

Table 2.2 Databases and sources searched and the date each search was completed

PubMed	15 May 2015
EMBASE (Ovid interface)	15 May 2015
CINAHL (EBSCOHost)	15 May 2015
Scopus	15 May 2015
Cochrane Central Trials Register	15 May 2015
Proquest Dissertations and Theses	15 May 2015
Current Controlled Trials (ClinicalTrials.gov)	15 May 2015
Australian New Zealand Clinical Trials Registry (anzctr.org.au)	15 May 2015

To increase the sensitivity of the search strategy, no limits relating to the publication type were applied. Studies were excluded following the citation review (see Section 2.2). The final refined search strategy was designed to capture the research papers relating to the review question, and is presented in full for each database in Appendix 3. In addition to the electronic search, a hand search of the reference lists of the included studies was performed.

2.2 Study selection

Citations returned from the database search, with details of the title, author, source and abstract, were saved and managed using EndNote™ (Version X6, Thomson Reuters, New York, USA) bibliographic citation management software. Duplicate citations were removed. Screening of the titles and abstracts was performed by the author of this thesis. Full-text manuscripts of potentially relevant citations were retrieved and assessed for eligibility against the review's inclusion criteria (see Section 1.13). The reference lists of all included reports and articles were hand searched to identify additional studies of relevance to the review. Although literature searching was performed independently by the author, a second reviewer (KU, Acknowledgements) was available to discuss any uncertainties regarding the inclusion of a particular paper into the final selection.

2.3 Critical Appraisal

Two independent reviewers assessed the methodological validity of papers that met the inclusion criteria using the Joanna Briggs Institute Meta-Analysis of

Statistics and Review Instrument (JBI-MAStARI), which was tailored to meet the objectives of the present review (Appendix 4). As no eligible experimental studies were located for inclusion in this review, the JBI appraisal tool for experimental/observational studies was not utilised (See Section 3.1 and the *a priori* protocol in Appendix 1).

The critical appraisal tool comprised nine questions that assessed the methodological validity of the selected studies (see Table 3.1 in Section 3.2). Each question was answered as either “yes”, “no”, “unclear” or “not applicable” according to the information provided in each paper. The answer “yes” indicated that the predetermined criterion was clearly identifiable in the paper and “no” if it was not. Criteria were marked as “Unclear” if inadequate information was provided by the study authors to enable a conclusive decision. Any incongruence in how the critical appraisal questions were interpreted or answered was resolved through discussion between the reviewers.

Question 7 was not applicable to retrospective studies as it refers to the outcomes of participants who withdrew from the study (Table 3.1); therefore, this criterion was not considered when assessment of the retrospective studies was performed. Consequently, retrospective studies were scored on an eight-point scale, while prospective studies were scored on a nine-point scale.

Studies that scored between zero and four out of eight/nine critical appraisal questions were considered to be low quality; studies that scored between five and six were considered to be medium quality; and those that scored between seven and eight/nine were considered to be of high quality. Given the limited number of studies that were located examining the effects of sedatives on cardiovascular and respiratory systems in patients diagnosed with OSA, those studies assessed and determined to be of low quality were not excluded from the final synthesis in this systematic review.

2.4 Data extraction

One reviewer extracted data from the included papers into a customised data extraction template (Appendix 5). Extracted data included the study design, the study’s country of origin, the research setting, patients’ characteristics and clinical

baseline data, the methods used to detect the presence or absence of OSA, the intervention (i.e. list of drugs used for sedation administration), and the outcomes of interest (Table 3.2 and Appendix 5). Extracted data also included details of patients' position during procedures, oxygen administration and the monitoring equipment used to measure patients' vital signs (see Table 3.2).

Details of how outcomes were defined were also extracted from each study and it was documented when outcomes of interest were not adequately defined or described. For example, in one study (Gill et al., 2011) desaturation was described as 'hypoxia' by the authors, but no description of 'hypoxia' was provided.

Additional information requested from Dr Mador (Mador et al., 2011) was sought to clarify the study results, patients' positions during procedures, and oxygen supplementation during sedation administration. No response from the author was received.

2.5 Data synthesis

Review Manager (RevMan) (Version 5.3; Copenhagen: the Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform meta-analysis on outcome data where possible. Odds ratios and 95% confidence intervals (CIs) of complication rates were calculated using a random effects model. Heterogeneity was assessed using χ^2 and I^2 tests. Statistical pooling was not possible for the following outcomes: hypertension, apnoea/snoring and hypoventilation, therefore the results were presented in a narrative synthesis with tables to aid in data presentation.

3. Results

Chapter 3 presents the results of the study selection process, the methodological quality assessment and characteristics of the included studies, and the synthesis of outcome data.

3.1 Process of study selection

A total of 4028 citations were identified through the search of included databases (see Section 2.1). After removal of duplicates, the titles and abstracts of the remaining 3835 unique records were screened for eligibility. Eighty full-text publications were retrieved and assessed against the eligibility criteria (see Figure 3.1). Of these, five studies were deemed eligible, underwent critical appraisal and were included in the review (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015). No experimental studies assessing and comparing the effects of propofol, midazolam and fentanyl for PSA were identified during the search (see Section 1.13). Studies that did not meet the eligibility criteria on full-text review are listed in Appendix 6, along with a brief description outlining the reasons for their exclusion.

The main reasons citations were excluded on full-text were: five conference abstracts (3 full-texts located); forty articles that did not contain primary data (e.g. discussion papers; letters and editorials; reviews; opinion statements and consensus papers); 12 studies with ineligible population (e.g. studies on pediatric patients, non-OSA or high risk for OSA patients); 4 studies with ineligible intervention (e.g. studies on OSA patients having surgery under general anaesthesia); 13 studies employed ineligible study design (e.g. studies without control or with no primary data available, studies on surgical treatment of OSA, reviews of screening instruments for OSA, sleep nasal endoscopy studies for the diagnosis of OSA); one article was excluded as full-text was not located (Appendix 6). The results of the full study selection and inclusion process are illustrated in Figure 3.1.

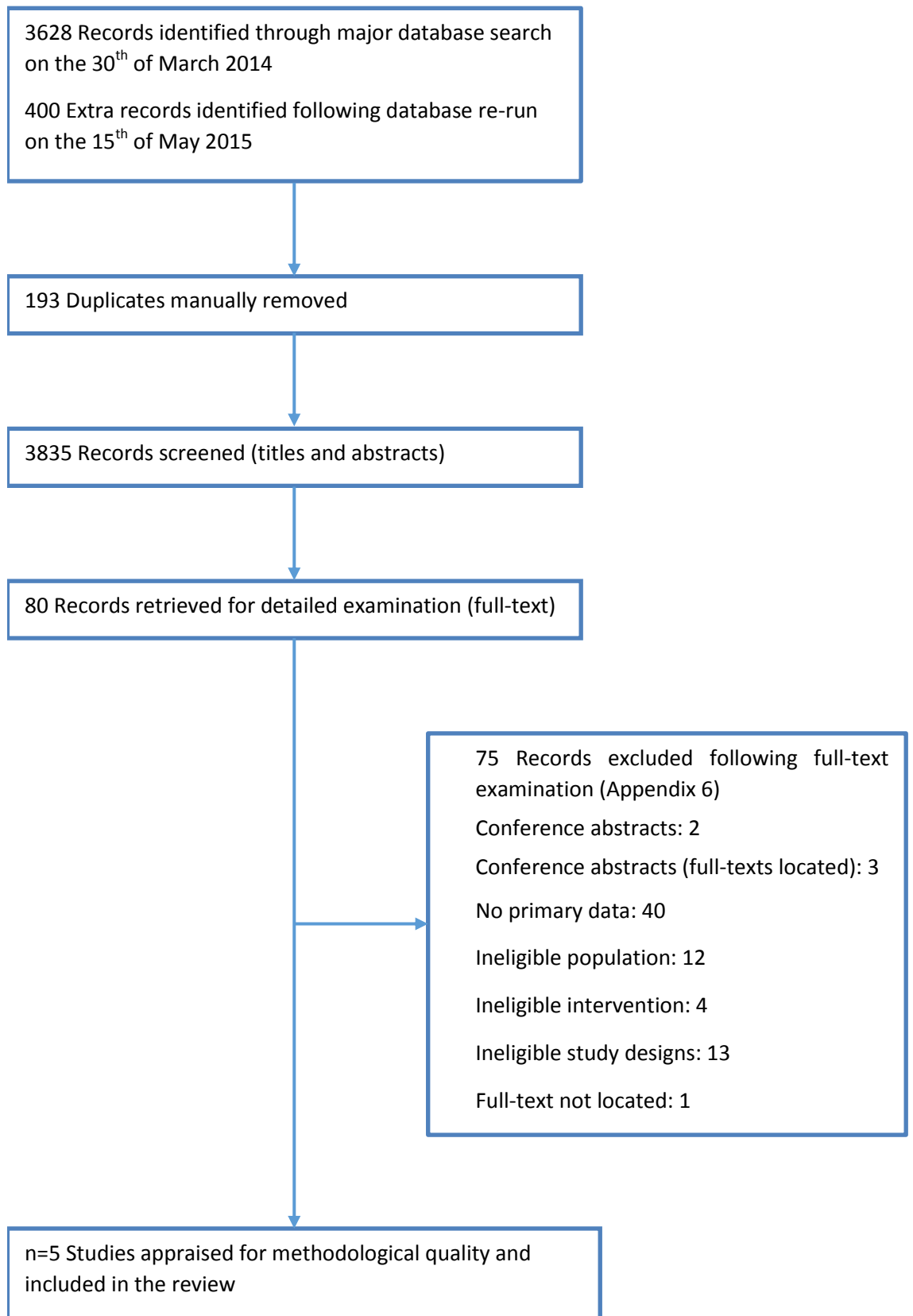


Figure 3.1 The study selection and inclusion process

3.2 Assessment of Methodological Quality

Overall, the included studies were of low to medium quality, scoring between two and five points out of a possible eight when assessed against the nine critical appraisal questions applicable to comparable cohort/case control studies (Appendix 4). Note: Question 7 was considered ‘Not Applicable’ for retrospective studies and was marked accordingly; see Section 2.3. The critical appraisal scores for each of the five included studies are outlined in Table 3.1.

One study (Adler et al., 2011) also included patients in their OSA group, who were diagnosed with OSA using portable home monitoring, or had a medical history and positive response to the use of CPAP. No further explanation or details of how many patients were confirmed by PSG or by other methods, was provided by the study authors. Therefore, ‘Q1’ was marked as ‘no’ for this particular study. Studies scored well on the question about patients being at a similar point in their condition (Q2) and described OSA subgroups according to AHI (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Andrade et al., 2015).

The included studies received low scores for the question related to the selection of cases and controls (Question 3). Selection criteria confirming the non-OSA status of patients in the control group were not stated in four out of the five studies (Adler et al., 2011, Gill et al., 2011, Cha et al., 2013, Andrade et al., 2015). Only one study allocated patients into the control group based on a negative overnight PSG study (Mador et al., 2011). As a result, four out of the five studies were at risk of bias when selecting participants for the non-OSA (control) group.

Studies generally scored well in response to Question 5, which queried whether the outcomes of interest were measured using objective criteria. The majority of studies provided a description of the monitoring used to assess oxygen saturation, blood pressure and heart rate, and also described and recorded any adverse events.

Table 3.1 Critical appraisal scores for the included studies

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total
Adler et al., 2011	N	Y	N	N	Y	N	N/A	N	Y	3/8
Andrade et al., 2015	Y	Y	U	U	Y	Y	N	N	Y	5/9
Cha et al., 2013	Y	N	N	N	Y	N	N	U	Y	3/9
Gill et al., 2011	Y	Y	N	U	U	N	N/A	N	N	2/8
Mador et al., 2011	Y	Y	Y	N	Y	N	N/A	N	Y	5/8
%	80	80	20	0	80	20	0	0	80	

Y = criteria achieved; N = criteria not achieved; U = criteria unable to be determined. Q7 does not apply to retrospective studies (shown as N/A). Total = possible points for prospective studies: 9, for retrospective studies: 8.

1. Is the sample representative of patients in the population as a whole?
2. Are the patients at a similar point in the course of their condition/illness?
3. Has bias been minimized in relation to selection of cases and controls?
4. Are confounding factors identified and strategies to deal with them stated?
5. Are outcomes assessed using objective criteria?
6. Is follow-up carried out over a sufficient time period?
7. Are the outcomes of people who withdrew described and included in the analysis?
8. Are outcomes measured in a reliable way?
9. Was appropriate statistical analysis used?

None of the studies reported on any observations beyond the post-procedure recovery period precluding the detection of delayed complications that might be associated with PSA. Therefore, all studies scored poorly on Question 6, which assessed whether follow-up was carried out over a sufficient period of time. Consequently, the longer-term (e.g. 24 hours post-PSA) adverse outcomes of PSA in OSA patients could not be assessed.

Question 7 was only assessed for two of the included studies (Cha et al., 2013, Andrade et al., 2015) that utilized a prospective study design. There was no explicit reporting in the prospective studies (Cha et al., 2013, Andrade et al., 2015) on the patients who might have withdrawn from the studies. Only one prospective study (Cha et al., 2013) reported on the OSA patients excluded from the study before starting enrolment. According to the study authors, patients refused to participate in the study due to sedation risks.

All five studies scored poorly on the reliability of methods used to measure respiratory and cardiovascular adverse event outcomes (Question 8). Comprehensive monitoring of respiratory function should include the monitoring of two components: oxygenation and ventilation. Oxygenation is the process of oxygen absorption across lung membranes and the delivery of oxygen to tissue cells. It is reflected by the arterial partial pressure of oxygen and is indirectly measured by pulse oximetry (Bhavani-Shankar et al., 1992). Ventilation refers to the mechanics of inspiration and expiration that moves gases, mostly carbon dioxide (CO₂) and oxygen in and out of the pulmonary system. Capnography is the graphic record of the CO₂ concentration in the expired gases during a respiratory cycle and an indicator of the changes of CO₂ elimination from the lungs (Bhavani-Shankar et al., 1992). Consequently, adverse events such as airway obstruction, hypoventilation and apnoea can easily be detected via capnography monitoring. Although oxygenation was measured by pulse oximetry across the included studies, the assessment of ventilation via capnography was not considered in any of the studies. Furthermore, all of the included studies used the term 'hypoxia' in their results. Strictly speaking, the diagnosis of hypoxia requires arterial blood gas measurements. It seems that the term hypoxia was used inappropriately in all the included studies as none of the included studies reported performing an arterial blood gas analysis.

Appropriate statistical analyses (Question 9) were used in four of the studies (Adler et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015); one study (Gill et al., 2011) did not report details of how their analysis was performed.

3.3 Characteristics of the included studies

The key characteristics of the included studies are described below and summarised in Table 3.2. Further descriptive details of the outcomes and their measurement are documented in Section 3.4.

All of the included studies (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015) were analytic observational studies investigating the association between diagnosed OSA and cardiovascular and respiratory complications with confirmed PSA. Three were retrospective cohort studies (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011) and two utilised a prospective cohort study design (Cha et al., 2013, Andrade et al., 2015).

As outlined in the *a priori* inclusion criteria (Gagolkina et al., 2014, Appendix 1) the intervention of interest was PSA with fentanyl, midazolam and propofol. An extensive search to locate studies that evaluated the administration of midazolam or fentanyl compared to propofol in patients with confirmed OSA was conducted; unfortunately, no experimental studies that compared the effects of fentanyl/midazolam to propofol in the OSA population were found.

Of the included studies, four were conducted in the United States (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Andrade et al., 2015) and one in South Korea (Cha et al., 2013). Participant selection included the recruitment of OSA patients from a sleep centre laboratory in one study (Cha et al., 2013) and the enrolment of patients directly from clinic populations in four studies (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Andrade et al., 2015), i.e. from the James A. Haley Veterans Affairs Hospital (USA) (Gill et al 2011, Andrade et al., 2015), the University of Utah Health Sciences Center (USA) (Adler et al., 2011), and the Buffalo Veteran Affairs Medical Center (USA) (Mador et al., 2011).

All five studies (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015) included patients who were undergoing upper/lower GI

endoscopy procedures such as esophagogastroduodenoscopy (EGD), colonoscopy and flexible sigmoidoscopy with PSA. The total number of participants included in this review was 1826 (OSA group, n=1079; non-OSA group, n=747). The sample size in the included studies ranged from 96 (Cha et al., 2013) to 639 (Mador et al., 2011) (see Table 3.2). The number of OSA patients included in the individual studies ranged from 31 (Cha et al., 2013) to 509 (Mador et al., 2011). In four studies, the study population predominantly consisted of male subjects (74%-97%) in both the OSA and non-OSA groups (Gill et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015) (see Table 3.2).

The included studies (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015) used various combinations of drugs to achieve procedural sedation. For example, one study stratified their results according to two different drug combinations: propofol/fentanyl and midazolam/fentanyl (Adler et al., 2011). Another study examined the effects of moderate sedation with midazolam administration (Cha et al., 2013). One study reported administration of conscious sedation with fentanyl and midazolam (Mador et al., 2011). One study listed and described the doses of midazolam, meperidine, fentanyl, and promethazine, which were administered to achieve conscious sedation (Gill et al., 2011). One study reported average doses of demerol, versed, fentanyl, and benadryl (Andrade et al., 2015). It was unclear whether a singular drug, or a combination of the aforementioned drugs, was used for sedation in two studies (Gill et al., 2011, Andrade et al., 2015).

Table 3.2 Characteristics of included studies

Citation	Study design Population Characteristics and baseline clinical data	Method to diagnose/detect OSA	Intervention	Description of outcomes as stated in the studies
Adler <i>et al</i> (2011) USA	<p>Retrospective pilot study.</p> <p>Retrospective chart review of patients who underwent elective esophagogastroduodenoscopy (EGD) and colonoscopy.</p> <p>OSA and non-OSA patients were identified via evaluation of endoscopic database from the most recent procedures and then working backwards over time, identifying OSA cohort participants first, and then a cohort of non-OSA patients for comparison. Aim of the study was to compare outcomes of OSA and non-OSA patients undergoing EGD and colonoscopy with nurse administered propofol sedation (NAPS) and conscious sedation (CS) with fentanyl and midazolam.</p> <p>Patients with OSA who received NAPS were compared to patients without OSA who received NAPS.</p> <p>Patients with OSA who received CS were compared to patients without OSA who received CS.</p> <p>All patients received supplemental oxygen (6 L/min) via nasal cannula:</p> <p>Total: N=215</p>	<p>Overnight PSG, or portable monitoring, or medical history and positive response to the use of CPAP.</p> <p>Methods of analysis to confirm absence of OSA in non-OSA (control) group not stated.</p>	<p>Sedation administration for elective EGD and colonoscopy with:</p> <p>1) fentanyl midazolam (conscious sedation (CS))</p> <p>2) propofol, sometimes with fentanyl (Nurse administered propofol sedation (NAPS)).</p>	<p>Hypotension (systolic BP <90), oxygen desaturation (oxygen saturation <90%), mean procedure time.</p> <p>Frequency of outcome measures and follow-up:</p> <p>Vital signs recorded every 5 minutes in the absence of complications, or deviations from normal.</p> <p>Authors stated that it is possible, episodes of desaturation or hypotension may not have been noted by nurses.</p> <p>No follow-up reported.</p>

<p>OSA: n=105 Non-OSA: n=110</p> <p>Characteristics of OSA group:</p> <p><u>OSA patients receiving NAPS</u>, (n=55) Age (years) 56 ± 14 Gender Male n=29 (53%) BMI (kg/m²) 38.8 ± 11 Bi-PAP use n=21 (38%)</p> <p><u>OSA patients receiving CS</u>, (n=50) Age (years) 57 ± 13 Gender Male n=35 (70%) BMI (kg/m²) 32.4 ± 7 Bi-PAP use n=4 (8%) P<0.001</p> <p><u>In all OSA patients:</u> ASA 1 - 4% ASA 2 - 90% ASA 3 - 6%</p> <p>Characteristics of non-OSA group:</p> <p><u>Non-OSA patients receiving NAPS</u>, (n=57) Age (years): 58 ± 15 Gender: Male n=33 (58%) BMI (kg/m²): 27.4 ± 6</p> <p><u>Non-OSA patients receiving CS</u>, (n=53) Age (years) 58 ± 17 Gender Male n=26 (49%) BMI (kg/m²) 27.2 ± 6</p>		<p>Four groups were formed for comparison:</p> <ol style="list-style-type: none"> 1. OSA patients receiving NAPS 2. OSA patients receiving CS 3. Non-OSA patients receiving NAPS 4. Non-OSA patients receiving CS <p>Before March 2007 CS with fentanyl and midazolam was used.</p> <p>After March 2007 NAPS was adopted.</p>	
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	<u>In all non-OSA patients:</u> ASA 1 - 16% ASA 2 - 60% ASA 3 - 17% ASA 4 - 1%			
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Citation	Study design Population Characteristics and baseline clinical data	Method to diagnose/detect OSA	Intervention	Description of outcomes as stated in the studies
Andrade <i>et al</i> (2015) USA	<p>Prospective cohort study.</p> <p>Male veteran population. Patients with confirmed OSA and without OSA (control) undergoing upper and lower GI endoscopy (colonoscopy, flexible sigmoidoscopy, EGD).</p> <p>Total: N=487 OSA: n=243 Non-OSA: n=244</p> <p>Characteristics in OSA group Mean age (years): 60.8 Gender: Male n=235, female n=8 Mean BMI (kg/m²): 34.64</p> <p>Characteristics in non-OSA group Mean age (years): 60.9 Gender: Male n=241, Female n=3 Mean BMI (kg/m²): 29.72</p>	<p>Polysomnography.</p> <p>Methods of analysis to confirm absence of OSA in non-OSA (control) group not stated.</p>	<p>Conscious sedation with demerol, versed, fentanyl, benadryl.</p>	<p>Tachycardia (heart rate \geq100 beats per minute), bradycardia (heart rate <60 beats per minute), hypotension (systolic/diastolic BP <90/60 mm/Hg), hypotension (mean arterial pressure. (MAP) <65 mm/Hg), hypoxemia (defined as measured blood oxygen saturation < 90%). Average dose of sedative used.</p> <p>Frequency of outcome measures and follow-up: Heart rate, blood pressure, and level of blood oxygen saturation electronically recorded at 3-minute intervals.</p> <p>No follow-up reported.</p>

Citation	Study design Population Characteristics and baseline clinical data	Method to diagnose/detect OSA	Intervention	Description of outcomes as stated in the studies
Republic of Korea	<p>Prospective, case control study.</p> <p>Patients with confirmed OSA and a control group (consecutive healthy patients) enrolled for routine Cha <i>et al</i> (2013)</p> <p>EGD examination.</p> <p>Total: N=96 OSA: n=31 Non-OSA: n=65</p> <p>Characteristics and baseline clinical data in OSA group:</p> <p>Age (years): 51.3 ± 9.6 Gender: Male n=23 (74.2%) BMI (kg/m²): 26.5 ± 3.0 Height (m): 167.1 ± 6.8 Weight (kg): 74.3 ± 11.2 Smoking: n=9 (29.0%) Drinking: n=11(35.5%) Charlson score (points): 1.0 ± 0.2 Hypertension: n=10 (32.3%) Diabetes mellitus: n=4 (12.9%) Systolic BP (mm/Hg): 127.6 ± 16.9 Diastolic BP (mm/Hg): 79.3 ± 10.6 SaO₂ (%): 97.6 ± 1.7</p>	<p>Overnight polysomnography.</p> <p>Methods of analysis to confirm absence of OSA in non-OSA (control) group not stated.</p>	<p>Sedation with midazolam (mg/kg).</p>	<p>Hypoxia (oxygen saturation <90% for at least 5 seconds), oxygen administration (when oxygen saturation level dropped to between 81% - 89% for more than 15 seconds, or below 80% more than 5 seconds), hypotension (Systolic BP <90 mm/Hg or a drop of more than 20 mm/Hg from baseline systolic blood pressure), snoring or apnoea, flumazenil administration, doses of sedation administered, sedation level achieved, target level of sedation achieved (time), paradoxical responses described as “hostility, rage and even physical violence necessitating the restraint of such patient after administration of midazolam.”</p> <p>Frequency of outcome measures and follow-up:</p> <p>Frequency of reporting of outcome measures not reported.</p> <p>Authors stated that “all patients were continuously monitored for blood pressure, oxygen saturation, respiratory</p>

	<p>Characteristics and baseline clinical data in non-OSA (control) group:</p> <p>Age (years): 47.1 ± 11.8 Gender: Male n=27 (41.5%) BMI (kg/m²): 23.1 ± 3.3 Height (m): 164.4 ± 8.0 Weight (kg): 62.6 ± 12.0 Smoking n=9: (13.8%) Drinking n=24: (36.9%) Charlson score (points): 1.0 ± 0.0 Hypertension: n=9 (13.8%) Diabetes mellitus: n=7 (10.8%) Systolic BP (mm/Hg): 114.3 ± 22.2 Diastolic BP (mm/Hg): 66.1 ± 14.4 Oxygen saturation (%): 98.0 ± 2.2</p> <p>From 61 eligible patients with confirmed OSA, the first 30 OSA cases were excluded before starting enrolment: patients refused to participate in the study due to sedation risks.</p>			<p>activity and electrocardiography during the procedure”.</p> <p>Follow-up not reported.</p>
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Citation	Study design Population Characteristics and baseline clinical data	Method to diagnose/detect OSA	Intervention	Description of outcomes as stated in the studies
Gill <i>et al</i> (2011) USA	<p>Retrospective cohort study.</p> <p>Study included endoscopic procedures such as colonoscopy, dilation, enteroscopy, and EGD.</p> <p>No routine oxygen supplementation administered during endoscopic procedures.</p> <p>Total: N=400 OSA: n=200 Non-OSA: n=200</p> <p>Characteristics in the OSA group: Gender: male n=195 (97.5%), female n=5 (2.5%) Mean age (years): 61.2 ± 9.8 Mean BMI (kg/m²): 33 ± 6.3 Severe OSA: n=123 Moderate OSA: n=77</p> <p>Characteristics in the non-OSA group: Gender: Male n=185 (92.5%), female n=15 (7.5%) Mean age (years): 61.8 ± 9.8 Mean BMI (kg/m²): 28.6 ± 6.1</p>	<p>Overnight PSG.</p> <p>Patients with moderate or severe OSA included in OSA group.</p> <p>Methods of analysis to confirm absence of OSA in non-OSA (control) group not stated.</p> <p>It is possible that patients with mild OSA were included in the non-OSA group.</p>	<p>Sedation with midazolam, fentanyl, meperidine, promethazine for upper endoscopies and colonoscopies.</p>	<p>Hypoxia (“patient’s oxygen saturation was briefly in the 80s (percentage), but returned to near 100% after oxygen supplementation via nasal cannula”). Authors stated that in the OSA group there were “no serious cardiopulmonary complications requiring intubation, reversal agents or admission to the hospital”.</p> <p>In the non-OSA group “no cardiopulmonary complications occurred in the control group”. Definition of cardiopulmonary complications was not provided. It was unclear what the authors were looking for.</p> <p>Computer generated endoscopy reports were retrieved and reviewed for complications such as arrhythmias, hypoxia and the need for intubation. It seems, that the endoscopist manually entered the data and created the report.</p> <p>Nurses notes were not available (for information on vital signs).</p> <p>Frequency of outcome measures and</p>

			<p>follow-up:</p> <p>Even though the authors stated that it is hospital protocol to continuously monitor oxygen saturation, and monitor blood pressure and heart rate every two minutes during endoscopy, only complications recorded by endoscopists in their reports were retrieved by the study authors.</p> <p>It is not clear, for example, if episodes of hypotension and/or desaturation were documented in the endoscopy reports.</p> <p>Significant risk of reporting bias in this study.</p> <p>Follow-up not reported.</p>
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Citation	Study design Population Characteristics and baseline clinical data	Method to diagnose/detect OSA	Intervention	Description of outcomes as stated in the studies
Mador <i>et al</i> (2011) USA	<p>Retrospective cohort study.</p> <p>Through electronic medical records, authors identified patients who had undertaken both a sleep study and an endoscopy procedure under moderate sedation. All patients who had upper endoscopy, colonoscopy, or a combined procedure (colonoscopy and upper endoscopy at the same time) under moderate sedation from 2002 to 2008 were linked with patients who had undergone a sleep study at the Buffalo VAMC between 2001 and 2008.</p> <p>63.5% of patients had a sleep study before the endoscopy, 36.5% of patients attended a sleep study after the endoscopy.</p> <p>Total: N=639 OSA: n=509 Mild OSA (AHI 5.0-15): n=135 Moderate OSA (AHI 15.1-30): n=125 Severe OSA (AHI>30): n=249 Non-OSA: n=130 (negative sleep study (AHI<5/h) Age: 60.2±10 Gender: Male/female, 594/45 (92.96/7.04%) BMI: 34 ± 9.5 CC index: 2.03 ± 1.8 Non-smoker: n=307 (48.04%)</p>	<p>Overnight polysomnography.</p> <p>Methods of analysis to confirm absence of OSA (control group) by overnight polysomnography.</p>	<p>Conscious sedation with fentanyl and midazolam.</p>	<p>Authors reported:</p> <p>(1) “Total minor cardiopulmonary complications”: hypotension (systolic BP <90 mm/Hg), hypertension (systolic BP >160 mm/Hg), bradycardia (heart rate <55 beats per minute), tachycardia (heart rate >100 beats per minute), oxygen desaturation below 90%, bradypnoea (respiratory rate <8 breath /minute).</p> <p>(2) “Minor complication” that required intervention including intravenous fluids, atropine, epinephrine, use of a reversal agent, up-titration of oxygen, use of CPAP machine, intubation, transfer to ICU, prolonged observation (greater than 1 hour).</p> <p>“If the patient’s vital sign was already in the abnormal range at baseline but endoscopist considered that it was still safe to perform the procedure, a ≥25% change from this baseline was required to be considered a minor complication.”</p> <p>(3) “Total major complications”: significant hypotension (not defined),</p>

	<p>History of smoking: n=332 (51.96%)</p> <p>Race: White: n=548 (85.76%) African American: n=67 (10.49%) Hispanic: n=1 (0.16%) Native Alaska: n=9 (1.41%) Others: n=1 (0.16%) Unknown: n=13 (2.03%)</p> <p>P-value Male/female: 0.27 White race: 0.21 Non-smoker: 0.33</p> <p>Characteristics and baseline clinical data in mild OSA group, n=135: Gender: Male/female, 124/11 (91.85/8.15%) Age: 60 ± 11.3 BMI: 33.7 ± 13.4 CC index: 2.1±2 Non-smoker: n=48 (42.96%) History of smoking: n=77 (57.04%)</p> <p>Race: White: n=113 (83.70%) African American: n=15 (11.11%) Hispanic: n=1 (0.48%) Native Alaska: n=3 (2.22%) Others: n=0 (0.00%) Unknown: n=3 (2.22%)</p>			<p>altered mental state / loss of consciousness, respiratory distress, significant intervention.</p> <p>Frequency of outcome measures and follow-up: Vital signs obtained every 5 minutes during the procedure and every 15 minutes for 1 hour after the procedure.</p> <p>No long-term follow-up reported.</p>
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<p>Characteristics and baseline clinical data in moderate OSA group, n=125:</p> <p>Age: 61.6 ±10.2 Gender: Male/female, 116/9 (92.80/7.20%) BMI: 33.7 ± 10.5 CC index: 2.1 ± 1.9 Non-smoker: n=64 (51.20%) History of smoking: n=61 (48.80%)</p> <p>Race: White: n=108 (86.40%) African American: n=10 (8.00%) Hispanic: n=0 (0.00%) Native Alaska: n=1 (0.80%) Others: n=0 (0.00%) Unknown: n=6 (4.80%)</p> <p>Characteristics and baseline clinical data in severe OSA group, n=249:</p> <p>Age: 60.8 ± 8.3 Gender: Male/female 237/12 (95.18/7.04%) BMI: 35.0 ± 7.5 CC index: 2 ± 1.8 Non-smoker: n=127 (51.00%) History of smoking: n=122 (49.00%)</p> <p>Race: White n=213 (85.54%) African American n=29 (11.65%) Hispanic n=0 (0.00%) Native Alaska n=5 (2.01%) Others n=0 (0.00%)</p>			
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	<p>Unknown n=2 (0.80%)</p> <p>Characteristics and baseline clinical data of negative sleep study group (non-OSA), n=130:</p> <p>Age: 58.4 ±10.5</p> <p>Gender: Male/female 117/13 (90.00/10.00%)</p> <p>BMI: 32.4 ± 7.49</p> <p>CC index: 1.8 ± 1.7</p> <p>Non-smoker: n=58 (44.62%)</p> <p>History of smoking: n=72 (55.38%)</p> <p>Race:</p> <p>White: n=114 (87.69%)</p> <p>African American: n=13 (10.00%)</p> <p>Hispanic: n=0 (0.00%)</p> <p>Native Alaska: n=0 (0.00%)</p> <p>Others: n=1 (0.77%)</p> <p>Unknown: n=2 (1.54%)</p>			
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OSA = obstructive sleep apnoea; BMI = body mass index; BP = blood pressure; CC = Charlson comorbidity index; NAPS = nurse administered propofol sedation; CS = conscious sedation; AHI = apnoea hypopnoea index; ASA = American Society of Anaesthesiology checklist; EGD = esophagogastroduodenoscopy.

3.4 Outcomes

All five included studies (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015) provided a description of how adverse events relevant to this review were measured and reported. Although the included studies reported on a range of outcomes, only those identified *a priori* (Gagolkina et al., 2014, Appendix 1) and detailed in Section 1.13 are reported here and include hypo/hypertension, brady/tachycardia, chest pain, hypoventilation and oxygen desaturation.

3.4.1 Cardiovascular events

Description of cardiovascular events and monitoring

Cardiovascular events, including hypotension, hypertension, bradycardia and tachycardia were outcomes of interest in four of the included studies (Adler et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015). Only one study reported on chest pain (Mador et al., 2011). Close monitoring of patient's vital signs, such as blood pressure and heart rate, is a minimum standard of care during medical procedures with PSA as changes in patients' blood pressure are expected following drug administration. An endoscopist and registered nurse monitored and assessed patient's blood pressure during procedures in the study by Cha et al., (2013) and it was reported that a nurse took blood pressure measurements in the study by Adler et al., (2011). It was unclear who undertook the monitoring and assessment of patient's vital signs (blood pressure and heart rate) in the remaining three studies (Gill et al., 2011, Mador et al., 2011, Andrade et al., 2015).

The frequency with which blood pressure was measured was variable and ranged from every 3 minutes (Andrade, et al., 2015) to every 5 minutes (Adler et al., 2011, Mador et al., 2011). In addition to this, Mador et al., (2011) measured blood pressure every 15 minutes for 1 hour after the procedure. Cha et al., (2013) did not provide details of how often blood pressure readings were taken during procedures. Gill and co-workers (2011) reported on complications that were documented by endoscopists in their electronic records; however, it was unclear if all episodes of hypotension/hypertension were recorded. The same authors reported that it was hospital protocol to monitor patient's blood pressure every 2 minutes during an endoscopic procedure, however, it was not clear if all events

were documented by the endoscopists in their electronic record, as nurses' notes where vital signs were recorded, were not available for review by the study authors. Adler et al. (2011) reported that it was possible episodes of hypotension may have been missed or not reported by the nurses in the study. In summary, it is possible, that not all cardiovascular adverse events were recorded in the studies by Gill et al., (2011) and in Adler et al., (2011). Regularly monitoring the vital signs of a sedated patient during any procedure is important, so that adverse events, such as low or high blood pressure, and slow or fast heart rate, can be immediately addressed. In the peri-operative period, it is reasonable clinical practice to monitor and document blood pressure at 3-5 minute intervals. Not knowing how often blood pressure was taken, makes it difficult to determine whether a patient has experienced a hypo/hypertensive adverse event.

Hypotension was defined as systolic blood pressure <90 mm/Hg in four studies (Adler et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015). One study (Cha et al., 2013) defined hypotension as systolic blood pressure <90 mm/Hg or a drop of more than 20 mm/Hg in systolic blood pressure from baseline. Andrade et al., (2015) defined hypotension as either a systolic or diastolic blood pressure of <90/60 mmHg, or mean arterial pressure <65 mmHg. Adler et al., (2011) differentiated their results reporting incidence of hypotension based on two different drug combinations namely propofol/fentanyl and midazolam/fentanyl (See Table 3.2).

Hypertension was described as systolic blood pressure of more than 160 mm/Hg and reported in one study (Mador et al., 2011). One study (Cha et al., 2013) reported hypertension as a medical diagnosis in the characteristics and baseline clinical data of the population of interest (Table 3.2). However, Cha and colleagues did not report any treatment for hypertension with antihypertensive drug therapy. Furthermore, no details by the authors were provided on whether the antihypertensive medications were taken on the day of the procedure, or not.

Continuous cardiac monitoring was used for monitoring patients' heart rate and rhythm for the presence of cardiac arrhythmias and was described in four studies (Adler et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015). Bradycardia was defined as a heart rate <55 beats per minute in the study by

Mador et al., (2011); while Andrade et al., (2015) defined bradycardia as a heart rate <60 beats per minute. Tachycardia (heart rate >100 beats per minute) was described and reported in two studies (Mador et al., 2011, Andrade et al., 2015).

Mador et al., (2011) reported minor and major cardiovascular complications. In their study, the minor complications were defined as hypotension, hypertension, bradycardia, tachycardia, desaturation and bradypnoea. Major complications were defined as chest pain, respiratory distress, cardio-respiratory arrest, or any minor complications that required intervention with intravenous fluid administration, atropine, epinephrine, the use of a reversal agent, up-titration of oxygen, use of CPAP therapy, intubation, a transfer to ICU, prolonged observation post-procedure, or unplanned admission.

Gill et al., (2011) did not provide definitions for cardiovascular complications, or what monitoring equipment was used during their study; however, the authors reported the absence of serious cardiopulmonary complications requiring intubation, reversal agents, or admission to hospital in both the OSA and control groups. See Table 3.3 for a detailed presentation of the cardiovascular events in the included studies.

Hypotension

Four studies (Adler et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015) reported the incidence of hypotension during PSA for GI endoscopy in OSA and non-OSA groups. Meta-analysis revealed no statistically significant difference between the OSA and non-OSA groups for hypotension (odds ratio = 0.95; 95% CI: 0.55-1.63) (see Figure 3.2).

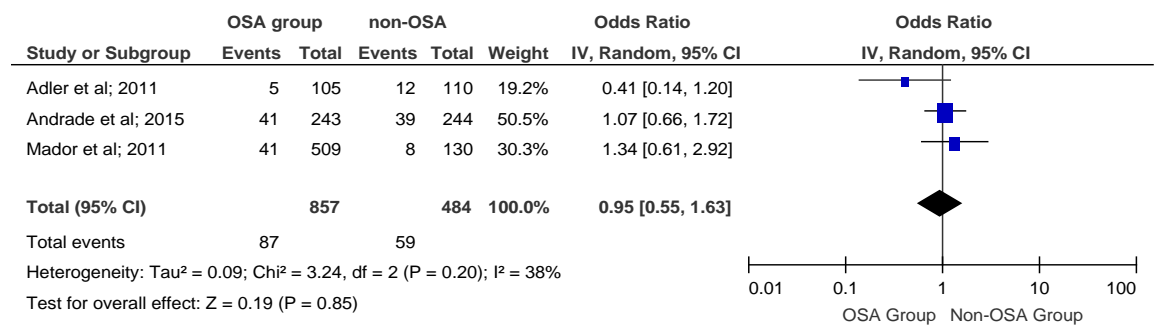


Figure 3.2 Odds ratio for hypotension in OSA and non-OSA groups

OSA = obstructive sleep apnoea.

Table 3.3 Cardiovascular events in OSA and non-OSA (control) groups

	OSA Group n/N (% of total events)	Non-OSA Group (control) n/N (% of total events)	P-value
Hypotension			
Adler et al., (2011) (Systolic BP<90 mm/Hg) Propofol/fentanyl	2/55 (3.63%)	8/57 (14.03%)	Not reported
Adler et al., (2011) (Systolic BP<90 mm/Hg) Midazolam/fentanyl	3/50 (6%)	4/53 (7.54%)	Not reported
Andrade et al., (2015) (Systolic/diastolic <90/60 mm/Hg)	41/243 (16.8%)	39/244 (15.9%)	0.460
Andrade et al., (2015) (MAP<65 mm/Hg)	16/243 (6.58%)	14/244 (5.73%)	0.571
Cha et al., (2013) (Systolic BP <90 mm/Hg or a drop of more than 20 mm/Hg from baseline systolic BP)	0/31 (0.00%)	0/65 (0.00%)	-
Mador et al., (2011) (Systolic BP<90 mm/Hg)	41/509 (8.06%)	8/130 (6.15%)	0.30
Hypertension			
Mador et al., (2011) (Systolic BP>160 mm/Hg)	34/509 (6.68%)	10/130 (7.69%)	0.73
*Bradycardia			
Andrade et al., (2015) (HR<60)	73/243 (30%)	83/244 (34%)	0.438
Mador et al., (2011) (HR<55)	6/509 (1.18%)	0/130 (0.00%)	0.25
Tachycardia			
Andrade et al., (2015) (HR>100)	19/243 (7.8%)	24/244 (9.83%)	0.749
Mador et al., (2011) (HR>100)	10/509 (1.96%)	4/130 (3.08%)	0.86

OSA = obstructive sleep apnoea; BP = blood pressure; MAP = mean arterial pressure; HR = heart rate; and reported in the included studies as 'beats per minute'.

*Note the difference in the definition of bradycardia.

None of the included studies, either individually, or when combined in meta-analysis (Figure 3.2) provide evidence for a statistically significant difference in

risk for hypotensive events between those with or without OSA. Observed statistical heterogeneity ($\chi^2 = 3.2$, $I^2 = 38\%$) could be explained by the methodological and clinical diversity across the studies included in the analysis.

Interestingly, the study by Cha et al., (2013) reported that none of their patients in either the OSA and non-OSA groups developed episodes of hypotension (Table 3.3). The authors of this study reported that ‘continuous monitoring’ and assessment of blood pressure on all patients during the procedure was provided. Strictly speaking, continuous blood pressure monitoring is possible only when an intra-arterial line is in place. Otherwise, blood pressure needs to be measured and reported according to established regular and rather frequent intervals. However, authors of this particular study failed to report how often, or how many, blood pressure readings were taken during the procedure. The patient’s blood pressure in between the measurements is unknown, therefore, it is possible, that episodes of hypotension were not detected in the study by Cha et al., (2013).

Another explanation of this could be the underlying diagnosis of hypertension in both the OSA and non-OSA groups of patients. Only one study (Cha et al., 2013) reported hypertension as a medical diagnosis in the characteristics and baseline clinical data of the population (Table 3.2). It is possible that patients with the diagnosis of hypertension had a reduction in their blood pressure, but it was not reported as hypotension because the values did not reach the definition that was applied by the study authors. Similarly, no details of antihypertensive therapy, or whether antihypertensive medications were taken on the day of procedure, were reported in the study by Cha et al., (2013). Four other studies did not report on patients’ medical history of hypertension (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Andrade et al., 2015).

Hypertension

Only one study reported hypertension as an outcome and concluded it to be a ‘minor complication’ in both control and OSA patients undergoing GI procedures with PSA (Mador et al., 2011). The study showed no significant difference in the number of documented events of hypertension as an adverse effect between the OSA and non-OSA groups (See Table 3.3).

Bradycardia

Two of the included studies reported bradycardia as an adverse event in both the OSA and non-OSA groups during PSA for endoscopic procedures (Mador et al., 2011, Andrade et al., 2015). However, a meta-analysis of the data from these two studies found no significant increase in the occurrence of bradycardia rates in the OSA population (odds ratio = 0.85; 95% CI: 0.58-1.25), (see Figure 3.3).

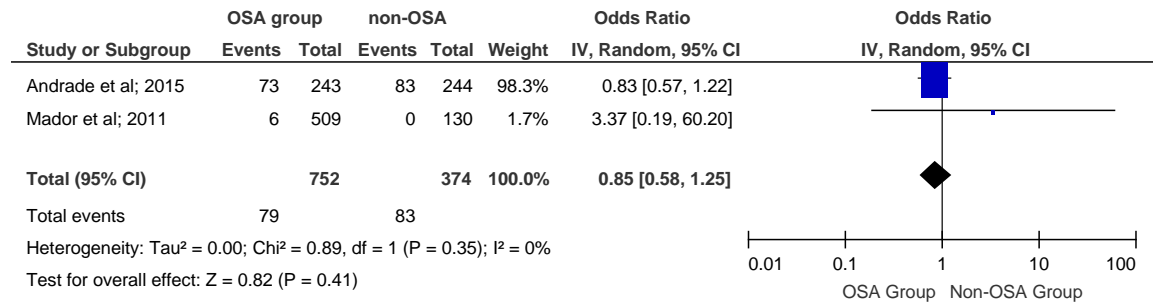


Figure 3.3 Odds ratio for bradycardia in OSA and Non-OSA groups

OSA = obstructive sleep apnoea.

There was a marked difference in the proportion of patients that experienced bradycardic events between these two studies (Mador et al., 2011, Andrade et al., 2015). Thirty percent of participants in the OSA group experienced bradycardic events in the study by Andrade et al., (2015), whereas only 1% of the OSA group experienced any bradycardic event in the study by Mador et al., (2011); (see Table 3.3, Figure 3.3). The difference in proportion is reflected in the weight attributed to each of the included studies in the analysis. Despite the absence of statistical heterogeneity in this analysis, it is worth noting both the clinical and methodological heterogeneity that underpins this result of the meta-analysis (Figure 3.3). The remarkably low bradycardia rates seen in the study by Mador et al., (2011) could be attributed to the difference in the definition of bradycardia in the two studies (see Table 3.3). The assumption could be made that in the study by Andrade et al., (2015) the heart rate dropped below 60, and while all events were recorded, no reports were available to see exactly how low the heart rate dropped in their study population. In contrast, Mador et al., (2011) reported only six events where the heart rate dropped below 55 in the OSA group. It is reasonable to speculate that Mador et al., (2011) observed a heart rate in the range of 55-60 more frequently, however it was not recorded as an adverse event in

their study.

Tachycardia

The incidence of tachycardia was described and reported in two studies (Mador et al., 2011, Andrade et al., 2015). Combination of the two studies in a meta-analysis revealed no statistically significant difference in the incidence of tachycardia between the OSA and non-OSA patient groups (odds ratio = 0.74 (95% CI: 0.43-1.29)) (see Figure 3.4).

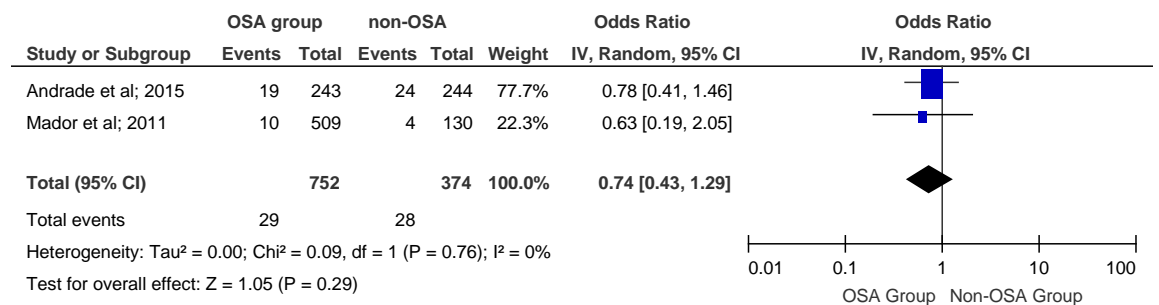


Figure 3.4 Odds ratio for tachycardia in OSA and non-OSA groups

OSA = obstructive sleep apnoea.

Though not as marked as the difference seen between these studies for bradycardia, the study by Andrade et al., (2015) reported a higher incidence of tachycardia than the study by Mador et al., (2011) (see Table 3.3). Since the definition of tachycardia was similar in both studies, the variation in the incidence of tachycardia between the two studies could be attributed to the differences in the frequency with which vital signs were recorded during the procedure. Mador et al., (2011) recorded heart rate every five minutes and reported fewer incidents of tachycardia in their study than Andrade et al., (2015) who documented heart rate more often (every 3 minutes) and reported a higher incidence of tachycardia.

Chest pain

Mador et al., (2011) reported that none of the patients in either the OSA or non-OSA groups developed an episode of chest pain or myocardial infarction during the GI endoscopies. The remaining four included studies (Adler et al., 2011, Gill et al., 2011, Cha et al., 2013, Andrade et al., 2015) did not evaluate or report on chest pain as an adverse event during PSA.

3.4.2 Respiratory events

Description of respiratory events and monitoring

Continuous pulse oximetry was used to measure oxygen saturation in all five studies (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015). Hypoxia was defined as oxygen saturation below 90% in four studies (Adler et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015). One study (Gill et al., 2011) did not provide a definition of hypoxia, despite reporting this outcome. In the study by Gill et al., (2011), the researchers were apparently measuring oxygen desaturation as estimated by pulse oximetry.

Overall, despite similar definitions of oxygen desaturation used by the authors of the included studies, there was no uniform practice in relation to the measurement of oxygen saturation. The frequency with which measurements of oxygen saturation were recorded varied between the included studies. As a result, a wide range of observations was reported in the included studies. Interestingly, while frequency of other vital signs, as discussed previously, were documented every 3-5 minutes, the oxygen saturation levels were not, except in two studies (Mador et al., 2011, Adler et al., 2011). However, authors in the study by Adler et al., (2011) stated that it was possible episodes of desaturation were not noted, or may have been missed by the nurses.

Bradypnoea was defined as a respiratory rate <8 breaths/minute in one study (Mador et al., 2011). Mador et al., (2011) did not define hypoventilation, but reported the incidence of hypoventilation in their results. It is uncertain if it can be assumed that bradypnoea was reported as hypoventilation in this study.

Table 3.4 Respiratory events in OSA and Non-OSA (control) groups

	OSA Group n/N (% of total events)	Non-OSA Group (control) n/N (% of total events)	P-value
Oxygen desaturation			
Adler et al., (2011)- Propofol/fentanyl (Oxygen saturation <90%)	1/55 (1.81%)	4/57 (7.01%)	Not reported
Adler et al., (2011)- Midazolam/fentanyl (Oxygen saturation <90%)	1/50 (2%)	2/53 (3.77%)	Not reported
Andrade et al., (2015) (Oxygen saturation <90%)	15/243 (6.17%)	15/244 (6.17%)	0.787
Cha et al., (2013) (Oxygen saturation <90%)	1/31 (3.2%)	7/65 (10.8%)	0.211
Gill et al., (2011) (No definition of oxygen desaturation is provided by the authors)	1/200 (0.5%)	0/200 (0.0%)	Not reported
Mador et al., (2011) (Oxygen saturation <90%)	12/509 (2.36%)	3/130 (2.31%)	0.63
Apnoea/Snoring			
Cha et al., (2013) No definition of apnoea provided by the authors	5/31 (16.1%)	7/65 (10.8%)	0.458
Hypoventilation			
Mador et al., (2011) No definition of hypoventilation provided by the authors	4/509 (0.79%)	0/130 (0.00%)	0.40

OSA = obstructive sleep apnoea.

Oxygen desaturation

All the included studies reported oxygen desaturation as a respiratory adverse event (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015). Interestingly, meta-analysis of the data from these studies did not demonstrate statistically significant differences between the OSA group and the non-OSA group (odds ratio = 0.84; 95% CI: 0.47-1.47) (see Figure 3.5).

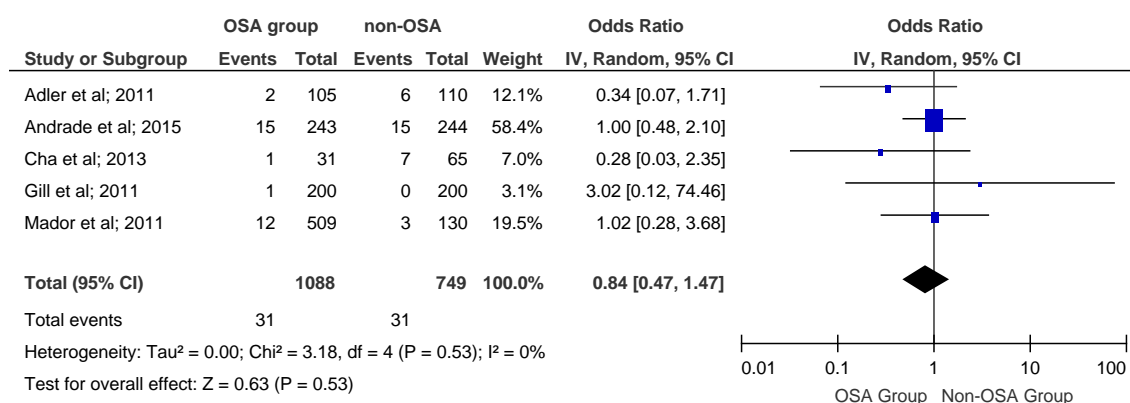


Figure 3.5 Odds ratio for oxygen desaturation in OSA and non-OSA groups

OSA = obstructive sleep apnoea.

Adler et al., (2011) differentiated their results on the basis of two different drug combinations, namely the propofol/fentanyl group and the midazolam/fentanyl group, and analysed those groups individually (see Table 3.4). Adler et al., (2011) reported that 6 L/min of supplemental oxygen via nasal cannula was administered to all patients during sedation administration. Therefore, it is possible that in the study by Adler et al., (2011), supplemental oxygen prevented the occurrence of oxygen desaturation events or conversely, the events of oxygen desaturation were not recorded.

The study by Gill et al., (2011) reported only one event of oxygen desaturation in the OSA group; while none were reported in the non-OSA group. These somewhat unusual results by Gill et al., (2011) could be attributed to the absence of a definition for hypoxia, or to the poor reporting on oxygen saturation levels in their study (see Table 3.1 and appraisal of question 8 in Section 3.2). It is difficult to determine without transparent reporting the presence or the absence of these events and whether events of oxygen desaturation actually occurred.

Apnoea or snoring

Apnoea, or snoring, was not defined but was reported in one study (Cha et al., 2013), (see Table 3.4). Four of the other included studies (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Andrade et al., 2015) did not report apnoea or snoring as an outcome of interest (Table 3.4).

Hypoventilation

Hypoventilation was reported, but not defined in one study (Mador et al., 2011) where, according to the authors, four out of 509 OSA patients (0.8%) developed hypoventilation. None of the patients in the non-OSA group developed this outcome (Table 3.4).

3.4.3 Complications requiring intervention

In the studies that reported on complications requiring intervention, the most common intervention reported was oxygen administration in response to oxygen desaturation (Table 3.5).

Table 3.5 Complications requiring intervention in OSA and non-OSA (control) groups

	OSA Group n/N (% of total events)	Non-OSA Group (control) n/N (% of total events)	P-value
Complications requiring intervention			
Andrade et al., (2015) (supplemental/prophylactic oxygen administration)	4/243 (1.64%)	4/244 (1.63%)	Not reported
Cha et al., (2013) (oxygen administration)	1/31 (3.2%)	1/65 (0.2%)	0.588
Gill et al., (2011) (oxygen administration)	1/200 (0.5%)	0/200 (0.0%)	Not reported
Mador et al., (2011) (administration of reversal agents, atropine, oxygen; CPR; use of CPAP/BiPAP; admission for observation)	37/509 (7.27%)	8/130 (6.15%)	0.41

OSA = obstructive sleep apnoea; CPR = cardiopulmonary resuscitation; CPAP = Continuous Positive Airway Pressure; BiPAP = Bilevel Positive Airway Pressure; both CPAP and BiPAP refer to the non-invasive form of therapy for treatment of OSA.

Cha et al., (2013) reported oxygen therapy administration as part of the ‘complications requiring interventions’ for oxygen saturation level dropping to between 81%-89% for more than 15 seconds, or below 80%. One study (Gill et al., 2011) did not define the term ‘hypoxia’ or under what conditions oxygen therapy would be administered. It is unclear when oxygen was administered in the studies by Mador et al., (2011) and Andrade et al., (2015).

Adler et al., (2011) reported that all patients received oxygen supplementation (for prophylaxis of oxygen desaturation) during the procedure. Notably, only 2/105 of OSA patients and 6/110 of non-OSA patients developed oxygen desaturation in the study by Adler et al., (2011). Two studies reported that no supplemental oxygen was administered to their patients during endoscopic procedure under sedation (Gill et al 2011, Cha et al 2013). It is not clearly reported in two other studies if supplemental oxygen was administered or not to their patients for GI endoscopies (Mador et al 2011, Andrade et al 2015).

One study (Mador et al., 2011) listed interventions such as administration of reversal agents, atropine, oxygen; CPR; use of CPAP/BiPAP or admission for observation. However, the authors of the study failed to detail the results for each intervention event separately. The remaining three studies (Gill et al., 2011, Cha et al., 2013, Andrade et al., 2015), did not report complications other than oxygen administration for low oxygen saturations.

Combination of the four included studies in meta-analysis found no significant difference in complications requiring interventions between the OSA and non-OSA groups, when the two groups were compared (Odds Ratio 1.23 (95% CI: 0.64-2.37); Figure 3.6).

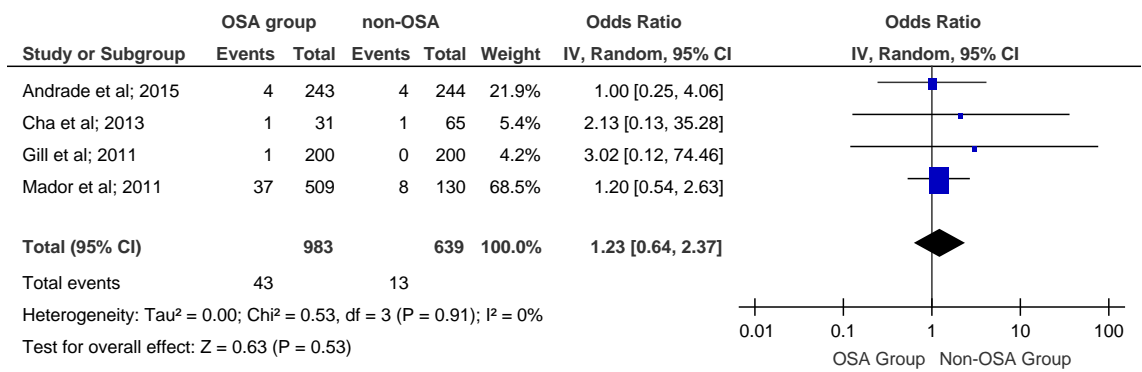


Figure 3.6 Odds ratio for complications requiring intervention in OSA and non-OSA groups

OSA = obstructive sleep apnoea.

In the study by Andrade et al., (2015), it is interesting to note that although the authors reported oxygen desaturation occurred in 15/243 OSA patients and in 15/244 non-OSA patients (Table 3.4; Figure 3.5), oxygen was administered to only four patients in each group (Table 3.5; Figure 3.6). In the study by Cha et al., (2013) the authors clearly described the conditions when oxygen was administered to their patients. During evaluation of their study results, one OSA patient who desaturated during the procedure, was administered oxygen therapy; compared to the non-OSA group, where only one of the seven patients received oxygen therapy for desaturation (Tables 3.4 and 3.5). One possible explanation for this might be that patients without OSA recover from desaturation faster, or that their oxygen desaturation was not sustained long enough to warrant the initiation of oxygen therapy.

Mador et al., (2011) did not provide an explanation of the circumstances when interventions were required, however they did report that any given patient could have more than one complication during their procedure; therefore, for this individual study, the total number of complications recorded may reflect repeated measurements in individual participants. Additional information was requested from the corresponding study author, Dr Mador (Mador et al., 2011), to help clarify the study results (specifically on when oxygen was administered to their patients), however no response from the author was received (see Section 2.4).

4. Discussion

Chapter 4 discusses the findings of this review with meta-analyses, which investigated the incidence of cardiovascular and respiratory adverse events associated with PSA in patients with confirmed OSA. Furthermore, this section highlights the limitations of the included studies, limitations of the present review, and the implications for practice and future research.

4.1 Findings

4.1.1 Key findings

The results of this systematic review found no statistically significant association between the diagnosis of OSA and PSA related complications. Several of the complications and adverse outcomes specified in the *a priori* protocol (Gagolkina et al., 2014, Appendix 1) were reported by the included studies. These included hypotension, hypertension, bradycardia, tachycardia, chest pain, oxygen desaturation, apnoea/snoring, hypoventilation and complications requiring intervention, such as oxygen administration or the administration of reversal agents or atropine. Similar drugs were administered to achieve PSA across the included studies; all the studies included the use of midazolam alone, or in combination with fentanyl for PSA (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015). One study also administered propofol alone, or with fentanyl (Adler et al., 2011).

As detailed in the *a priori* protocol (Gagolkina et al., 2014, Appendix 1) the intervention of interest was PSA with fentanyl, midazolam and propofol. The objective was to compare the safety of the drugs when used for PSA in patients formally diagnosed with OSA. Unfortunately, as no experimental studies were found that compared the effects of fentanyl/midazolam to propofol in the OSA population it was not possible to compare the incidence of adverse events between the nominated drug groups and therefore determine whether one drug type was safer to administer to OSA patients than another.

This systematic review was not limited to one particular procedural setting but aimed to include all possible medical or surgical procedures performed under

sedation on patients formally diagnosed with OSA. As outlined in the *a priori* protocol (Gagolkina et al., 2014, Appendix 1), procedures that can be performed under PSA include, but are not limited to, GI endoscopy, bone marrow biopsy, cardiac studies, bronchoscopy, minor plastic surgery, vascular stenting and urological procedures. Given that only studies conducted with patients undergoing GI endoscopies were identified, the findings of this review are based on the endoscopic population and not on the general patient population including those presenting to healthcare facilities for other medical or therapeutic procedures.

Notably, this review only included studies involving patients formally diagnosed with OSA. Conversely, a systematic review performed by Gaddam et al., (2015) (discussed in Section 1.1), included patients with OSA and those at high risk of OSA using the STOP-BANG questionnaire and reported similar drugs used for PSA. The authors acknowledged the potential for misclassification of patients into high or low risk OSA groups based only on the questionnaire. Interestingly, despite the difference in inclusion criteria, the results of the systematic review outlined in this thesis are similar to those reported by Gaddam et al., (2015), who also found no increase in post-endoscopy complication rates in patients with OSA or in patients at high risk of OSA when compared to patients without OSA or those at low risk of OSA.

The author's working hypothesis was that individuals diagnosed with OSA are at risk of developing cardiovascular and respiratory adverse events following PSA, possibly as a result of a combination of anatomical factors and drug administration. In addition, as outlined in Section 1.1, OSA is associated with a variety of medical conditions, including hypertension, diabetes, cardiac arrhythmias and cardiovascular disease, and hence there is increased likelihood of the development of peri-operative complications. Surprisingly, the findings of this review demonstrated no difference in the incidence of respiratory and cardiovascular adverse events between the confirmed OSA and non-OSA groups with PSA.

4.1.2 Overview of cardiovascular outcomes

The present review identified three cardiovascular outcomes (hypotension,

bradycardia and tachycardia) with sufficient data to be combined in a meta-analysis. Although four studies reported on hypotension (Adler et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015), the meta-analysis on this outcome only included three studies, as one study (Cha et al., 2013) reported no events of hypotension in either the OSA or non-OSA group.

This review found no statistically significant association between OSA and hypotension. First, this could be attributed to the frequency of reporting for this outcome (the importance of careful reporting of blood pressure is discussed in Section 3.4.1). Second, the pre-existing diagnosis of hypertension may have played an important role, however, none of the included studies reported on whether patients took their usual antihypertensive therapy on the day of PSA. It is possible that patients with a diagnosis of hypertension who took regular therapy did not take it on the day of the procedure. As such, these patients may have lowered their blood pressure following sedative administration but the measured blood pressure values did not reach the values defined as hypotension in the studies and as a consequence, a low incidence of hypotension was reported. Ideally, hypotension should be described as a change from the patient's baseline blood pressure rather than a pre-set cut-off value. How this outcome was measured in the included studies could potentially lead to false blood pressure readings and therefore limit the validity of the findings (see Section 4.2.2).

Adverse events involving bradycardia and tachycardia were reported in two studies (Mador et al., 2011, Andrade et al., 2015). No statistically significant increase in the incidence of bradycardia and tachycardia between OSA and non-OSA patients was found when both studies were pooled for meta-analysis (see Section 3.4.1). However as mentioned in Section 3.4.1, the authors employed different definitions of bradycardia in their studies. For example, Mador and colleagues (2011) defined bradycardia as a heart rate of 55 beats per minute, while Andrade et al., (2015) defined the same outcome as 60 beats per minute. The differential definition of bradycardia between the two studies may have influenced the results of the meta-analysis and thus caution should be exercised when interpreting the meta-analysis results for this outcome.

Although the definition of bradycardia was different in studies that reported on

this outcome (Mador et al., 2011, Andrade et al., 2015), the definition of tachycardia was identical in both studies and described as 100 beats per minute. A vast difference in the incidence of tachycardia between the two studies was noted. This finding could be explained by the difference with which the frequency of the heart rate was recorded during the procedure. Greater incidence of tachycardia was reported in the study by Andrade et al., (2015), who documented heart rate every 3 minutes, compared to the study by Mador et al., (2011), who recorded heart rate every five minutes. Additional studies with well-defined outcome measurements are required before conclusions can be drawn on whether or not bradycardia and tachycardia are associated with OSA following PSA administration.

Hypertension and chest pain could not be aggregated as these adverse outcomes were only reported by one eligible study (Mador et al., 2011). Although no events of chest pain was reported by the authors, hypertension was reported (see Section 3.4.1, Table 3.3). An increase in blood pressure during the procedure in this study could be explained by the pre-existing diagnosis of hypertension; however this was not reported by the authors. Another explanation for the reported hypertension could have been due to the discomfort or pain the patient experienced during the endoscopic procedure. Therefore, pre-existing hypertension should be considered in future studies as it can potentially alter the results of study outcomes.

4.1.3 Overview of respiratory outcomes

Oxygen desaturation was the most commonly reported adverse outcome in the included studies. While no statistically significant association between OSA and oxygen desaturation with PSA was observed, there appeared to be a trend towards decreased odds of oxygen desaturation in the OSA group when study data was combined statistically. The wide confidence intervals in the included studies could be explained by the low incidence of oxygen desaturation events. For example, one study reported the possibility that desaturation events may have been missed or not noted by nurses and therefore were not reported (Adler et al., 2011). Another explanation for the wide confidence intervals could be the lack of large studies available to show the effect.

Similar to the results of this review, Gaddam and colleagues (2015) reported no statistically significant association with oxygen desaturation in patients diagnosed with OSA or those at high risk for OSA undergoing diagnostic upper and lower endoscopy, screening colonoscopy, ERCP and EUS. Despite the lack of statistical significance, the inclusion of studies with participants at high risk of OSA however did appear to result in a larger effect size than reported here with PSG confirmed OSA (see Gaddam et al., 2015; Figure 2). Moreover, the inclusion of patients at high risk of OSA may have increased the likelihood that the OSA group contained non-OSA patients, which could explain the statistically significant heterogeneity was observed in the Gaddam et al., (2015) meta-analysis.

Another explanation for the low incidence of oxygen desaturation across the included studies could be due to the administration of prophylactic oxygen to patients diagnosed with OSA that prevented oxygen desaturation. One study (Adler et al., 2011) clearly described that 6 L/min of oxygen was administered to all patients receiving PSA during GI endoscopies, while in two studies (Mador et al., 2011, Andrade et al., 2015) it was not clear whether or not oxygen was administered to patients to prevent oxygen desaturation (the impact of oxygen supplement on oxygen desaturation is discussed in detail in Section 4.2.3).

Lastly, lateral or prone patient positioning during GI endoscopy could have played a role in a small number of oxygen desaturation events (the effect of body position on OSA is discussed in Section 1.2.5). As discussed in the Section 1.2.5, patients in a lateral or prone body position have reduced AHI and therefore, can be considered in the safest position for the maintenance of patent airway during sleep and PSA. Obstructive sleep apnoea predisposes upper airway to collapsibility when an individual is most relaxed. Administration of propofol, midazolam and fentanyl for PSA results in sedation and muscular relaxation and as described earlier in Section 1.9, these drugs are associated with respiratory complications such as airway obstruction and oxygen desaturation. The studies included in this review targeted adverse respiratory outcomes such as oxygen desaturation and bradypnoea, but did not include adverse events such as airway obstruction or apnoea that may lead to oxygen desaturation. Thus, it is possible

that important adverse respiratory events were not monitored and consequently, were not detected and not reported in the included studies. The methodological weaknesses of the included studies as described in Section 3.2 undermine the validity of the study results.

4.1.4 Evidence on the association between adverse events and use of sedatives

During the literature search for this review it became evident that extensive research has been undertaken investigating PSA for diagnostic and therapeutic procedures. While not many studies were located that met the specific population inclusion criteria for this systematic review (see Section 1.13), similar studies that reported an association between adverse events and the use of sedatives in patients undergoing GI endoscopy procedures from the general adult population were identified (Qadeer et al., 2011, Lera dos Santos et al., 2013).

The results from these studies contradicted the findings from the review presented in this thesis. For example, in the study by Lera dos Santos et al., (2013), 42% of the participants receiving propofol-fentanyl and 26% of those receiving fentanyl-midazolam for upper endoscopy developed transient hypoxemia (defined as oxygen saturation between 85-90% for more than 30 seconds following jaw thrust manoeuvre), and required an oxygen supplement. In contrast, 1.81% of patients in the OSA group and 7.01% in the non-OSA group who received propofol-fentanyl in the study by Adler et al., (2011) developed oxygen desaturation, while 2% of patients in the OSA group and 3.77% in the non-OSA group who received fentanyl-midazolam dropped their oxygen saturation.

Moreover, in a randomised trial of ventilation monitoring during endoscopic procedures such as EUS and ERCP, Qadeer et al., (2011) reported hypoxaemic events in 123 control patients. Hypoxaemia occurred in 35% of the patients within one minute, and in 85% of the patients within 5 minutes, following sedation administration and/or endoscopic intubation. Hypoxaemia during the EUS was associated with normal ventilation in 90.5% of cases, and in 71.5% of patients with abnormal ventilation. In contrast, the incidence of oxygen desaturation during PSA in patients with confirmed OSA undergoing similar procedures in the included studies ranged from 0.5% to 6.17%, whereas the incidence of the same events in non-OSA patients ranged between 0% and 10.8% (see Table 3.4). The

difference in the results could be attributed to the nature of the endoscopic procedures performed in the included studies. Qadeer and co-workers (2011) hypothesised that high rates of hypoxaemia during EUS could be related to the multiple endoscopic intubations used in every patient and the large diameter instruments used for EUS.

Overall, considering such high complication rates during PSA are observable in the general population, it would be expected that higher adverse events rates would be observed in the OSA population. If patients in the included studies had more intubations, and/or larger instruments were used during GI procedures, the incidence rates in OSA group would be higher. Nevertheless, more studies including complex endoscopic procedures are required to make certain conclusions.

The results of the prospective study by Cote et al., (2010) on patients undergoing GI endoscopies, which focused on patients at high risk for OSA and therefore did not meet the inclusion criteria for this review (see details in Appendix 6) are noteworthy. The authors reported that 12.1% of participants, all of whom were in the STOP-BANG positive group (scored three points or higher out of a possible eight points on the STOP-BANG tool; see Appendix 2) experienced adverse effects that resulted in them requiring airway support (Cote et al., 2010). For example, two of these patients developed apnoea; one patient developed upper airway obstruction and required bag-mask ventilation; 12 patients needed a chin lift manoeuvre; 12 patients required the use of a customised high oxygen delivery system (modified mask airway); and 10 patients needed nasal airway insertion. Hypoxemia (defined as pulse oximetry of <90%) was recorded in 12 patients and apnoea was reported in two cases. As well as the high proportion (43%) of STOP-BANG positive patients admitted for GI endoscopic procedures, this study also demonstrated that the frequency of hypoxaemic events was significantly higher among STOP-BANG positive patients than among STOP-BANG negative patients (Cote et al., 2010).

There could be several explanations as to why the findings from the study by Cote et al., (2010) contradicted the results of this review. Cote et al., (2010) studied patients undergoing upper GI procedures such as ERCP and EUS. Conversely,

endoscopic procedures such as colonoscopy, diagnostic EGD and combined procedures were performed in the included studies (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015), which are less painful procedures compared to ERCP (Goulson and Fragneto, 2009) and require a lower level of sedation to complete the procedure. Consequently, less drugs need to be administered during endoscopic procedures to achieve the desired level of sedation. In contrast, ERCP could be described as a prolonged, invasive and uncomfortable procedure, often performed on acutely unwell patients with pancreatitis, pancreatic cancer and/or cholangitis (Goulson and Fragneto, 2009). Therefore, patients undergoing ERCP are likely to be in poorer health, and more sensitive to the sedatives administered and/or may require more drugs during the stimulating and painful endoscopic procedure. As a result, the risk of unwanted adverse events during ERCP procedures could be higher compared to other endoscopic procedures such as EGD or colonoscopy.

4.1.5 Patient's position during endoscopy

The patient's position during the procedure was a strong confounding factor that needed to be considered when discussing the adverse events on patients receiving PSA. Surprisingly, none of the reviewed studies reported patients' positions during the endoscopic procedures. All of the included studies were designed and performed on patients undertaking diagnostic, therapeutic or combined upper and lower endoscopy, screening colonoscopy, ERCP and EUS. Patients undergoing EU or colonoscopy procedures are generally placed in the left lateral decubitus position, while patients undergoing ERCP are typically in a prone or semi-prone position (Das, 2008, Wilcox, 2008). Therefore, it is quite possible, that the low incidence of adverse respiratory events in the included studies could be due to patients' lateral or prone position during the GI endoscopies. However, the question remains open as to whether patients placed in the supine position would have a higher incidence of respiratory complications or not.

4.2 Limitations of the included studies

4.2.1 Differences in patient characteristics

There was a lack of clear and consistent criteria for determining the non-OSA group participants across the included studies. Although the method of selecting

participants for the OSA group was satisfactory in all five studies, four studies did not provide a clear definition of how the non-OSA group (the control group) was selected (Adler et al., 2011, Gill et al., 2011, Cha et al., 2013, Andrade et al., 2015). Only one study allocated patients' to the control group on the basis of a negative OSA result determined by an overnight PSG (Mador et al., 2011). As such, it is possible that not all patients in the control group across the remaining studies were negative for OSA.

It is also possible that undiagnosed OSA in the control group is a key factor underlying the absence of the hypothesised differences in the adverse event rates reported in this review and meta-analysis. Whilst it was hypothesised that patients without OSA would develop adverse events less often, compared to confirmed OSA patients, surprisingly, a slightly increased incidence of complications was reported in the non-OSA group in one study (Adler et al., 2011). Adler et al., (2011) reported 3.6% of OSA patients and 14% of non-OSA patients respectively developed hypotension when propofol and fentanyl were administered. In the same study, two out of 55 patients with OSA, compared to four out of 57 non-OSA patients developed oxygen desaturation during propofol and fentanyl administration. Similarly, another study (Cha et al., 2013) also reported a slight increase of oxygen desaturation events in the non-OSA group (10.8%) compared to the OSA group (3.2%). This interesting and unexpected observation in these two studies could be explained by the fact that patients allocated into the non-OSA group were not adequately screened for OSA.

Another issue that arose during the course of undertaking this review was the question of clinical heterogeneity of the patients selected for the OSA group. For example, Mador et al., (2011) categorised OSA patients into four subgroups according to their AHI: OSA negative, mild OSA, moderate OSA and severe OSA groups. Cardiopulmonary complications during and after endoscopic procedure under sedation were defined and classified into two groups: minor and major complications. The authors presented their results on complication rates into "negative" and "positive" sleep study groups. Subsequently, the authors combined all the OSA patients and placed them into one OSA group, creating a heterogeneous OSA group. Consequently, it is difficult to conclude the

significance of severity of OSA on patient's outcomes.

4.2.2 Outcome assessment

Measurement and reporting of outcomes

Inconsistencies in the identification, measurement and reporting of relevant outcomes in the included studies could have affected the results observed in this review and meta-analysis. Four studies measured hypotension using systolic blood pressure (Adler et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015). One study measured and recorded both systolic blood pressure and mean arterial pressure to identify hypotension (Andrade et al., 2015). Hypotension was defined as systolic blood pressure of less than 90 mmHg in four studies (Adler et al., 2011, Mador et al., 2011, Cha et al., 2013, Andrade et al., 2015). Hypertension was reported in only one study (Mador et al., 2011), and was defined as systolic blood pressure above 160 mmHg. However, using this simplified definition of hypo/hypertension, may lead to systematic error in how the results are recorded as participants with similar baseline blood pressure may have been inadvertently placed into one of these 'adverse events' categories.

The same caveat applies in the reporting of bradycardia. A heart rate of 50 beats per minute can be the norm for certain patients. For example, it is common for healthy individuals who exercise regularly to have a heart rate of 50 (or below) beats per minute. Furthermore, the presence of bradyarrhythmias such as sinus bradycardia, first-degree atrioventricular block, Wenckebach second-degree atrioventricular block in healthy athletes has been well discussed and reported in numerous studies (Talan et al., 1982, Pilcher et al., 1983, Zehender et al., 1990). Information on patients who are receiving beta-blockers and undergoing the procedure with existing bradycardia should have been carefully documented and reported in the studies. Again, it would have also been more appropriate to report on a deviation from the baseline heart rate, rather than on the basis of the established definition of bradycardia.

As mentioned, oxygen desaturation was the most commonly evaluated respiratory outcome. It is recommended practice to monitor oxygen saturation when administering sedatives to patients (Waring et al., 2003, Vargo et al., 2012). The included studies measured oxygen saturation via pulse oximetry monitoring and

reported oxygen desaturation, which was defined in three studies as oxygen saturation below 90%. While the definition of oxygen desaturation was similar in four of the included studies, the frequency of recording was not. Gill et al., (2011) in their retrospective study reported that nurses' notes were not available for review and therefore critical information such as mean saturation, total endoscopy time, and time to discharge was unavailable. Authors reported on one event of hypoxia in their results, but no definition of hypoxia was provided (Gill et al., 2011). In addition, the authors reported that patients' oxygen saturation was briefly in the 80s (percentage), but returned to near 100% after oxygen supplementation via nasal cannula (Gill et al., 2011, p.186). Poor reporting of oxygen saturation in the Gill et al., (2011) study could potentially lead to an underestimation of the results.

Outcomes that were not reported

Outcomes such as apnoea and airway obstruction were not mentioned or reported in four of the reviewed studies (Adler et al., 2011, Gill et al., 2011, Mador et al., 2011, Andrade et al., 2015). Therefore, it may be that these important respiratory complications were not monitored during PSA in those included studies. The term 'obstructive sleep apnoea' intrinsically infers "obstruction" (of the airways) might be taking place. However, only one study (Cha et al., 2013) reported amongst their outcome measures 'snoring or apnoea', where 'snoring' could be attributed to partial airway obstruction. The authors created one group of adverse events, 'snoring and apnoea'; however no definition of snoring or apnoea was provided in their study.

It is important to note here that while the reviewed studies monitored and reported oxygen desaturation, none of the studies looked at the causes leading to oxygen desaturation. None of the studies monitored patients' ventilation. No information on the respiratory rate or the depth and pattern of breathing was available from the included studies. All five studies failed to report monitoring of carbon dioxide via capnography. Capnography is the graphic record of carbon dioxide concentration in the expired gases during a respiratory cycle and an indicator of the changes of the carbon dioxide elimination from the lungs (Bhavani-Shankar et al., 1992). Capnography can be used to assess ventilatory parameters and also the

patency of the airway, as complete or partial airway obstruction will lead to a change or loss of the carbon dioxide trace on the capnograph (Bhavani-Shankar et al., 1992). Thus, capnography monitoring is essential for early detection of apnoea and/or airway obstruction. Respiratory events such as hypoventilation (shallow breathing), hypopnoea (slow respiratory rate), apnoea (cessation of breathing), and airway obstruction are potential complications that can be overlooked if the patient is not properly monitored via capnography during supplementary oxygen therapy with PSA. Furthermore, without capnography monitoring it is difficult to distinguish how apnoea was identified in the study by Cha et al., (2013). Despite mentioning apnoea as an outcome of interest, Cha and colleagues (2013), did not provide adequate monitoring of apnoea via capnography.

Despite these points mentioned, there are limitations of carbon dioxide monitoring during endoscopic procedures on sedated, non-intubated (breathing spontaneously without artificial airways) patients, as it is difficult to measure end tidal carbon dioxide gas accurately through a face mask or nasal cannula (Bhavani-Shankar et al., 1992). Nevertheless, utilisation of capnography during PSA would be considered a safe and prudent practice. Safe sedation requires capnography monitoring so that the breathing pattern can be observed and early intervention applied in the early stages of airway hypoventilation or obstruction before patients become significantly hypoxaemic. Therefore, it is possible that apnoea events were missed and, consequently not recorded and not reported in the included studies.

4.2.3 The role of oxygen administration and monitoring of respiratory function

All studies reported monitoring oxygen saturation and oxygen desaturation, however, the majority of the studies did not clearly report on the administration of supplemented oxygen during PSA. It is important to note that oxygen desaturation during GI endoscopy, with or without sedation, is a common occurrence (Reed et al., 1993, Wang et al., 2000, Rozario et al., 2008). Conversely, sedation increases the incidence of oxygen desaturation (Wang et al., 2000). Wang et al., (2000) reported that in the absence of supplemental oxygen, mild desaturation (defined

as oxygen saturation below 94%) occurred in 53.3% of patients sedated with midazolam, and hypoxia (defined as oxygen saturation of 92% or below for the duration of 15 seconds or longer) occurred in 23.3% of these patients. The study found that in the group where supplemental oxygen at 4 L/min via nasal cannula was administered, no episodes of oxygen desaturation occurred (Wang et al., 2000). A study by Rozario et al., (2008) also supports the routine use of oxygen supplementation for patients undergoing GI endoscopy with sedation. Rozario et al., (2008) found that patients who received supplemental oxygen at 2 L/min (experimental group, n=194) for GI endoscopy were 98% less likely to have oxygen desaturation than patients who did not receive supplemental oxygen (control group, n=195). Moderate sedation with fentanyl and midazolam, or fentanyl and diazepam, was administered to all patients. In the control group 70.8% (138/195) of patients experienced a desaturation episode compared to 12.4% (24/194) of patients in the experimental group ($p > 0.00001$) (Rozario et al., 2008).

A systematic review and a meta-analysis by Mehta et al., (2013) that examined the effects of oxygen on AHI in OSA patients who received oxygen therapy and CPAP treatment concluded that oxygen therapy significantly improves oxygen saturation in patients with OSA (Mehta et al., 2013). Earlier studies have also demonstrated that the administration of supplementary oxygen prevents hypoxia, but it does not prevent the occurrence of airway obstruction or impaired respiration when narcotic analgesics are administered (Jones et al., 1985).

Similarly, in the included study (Adler et al., 2011) where all patients received supplemental oxygen (6 L/min via nasal cannula) during PSA, 2% of OSA patients and 3.77% of non-OSA patients in midazolam/fentanyl group developed oxygen desaturation. The other two studies (Mador et al 2011, Andrade et al 2015), did not clearly report whether prophylactic oxygen supplementation was administered during PSA or not. However, if supplemental oxygen was administered to patients in the reviewed studies it would have protected those patients from oxygen desaturation. Oxygen saturation is not an overly sensitive marker of respiratory problems, especially when supplemental oxygen is used. It is likely, that even with airway obstruction or apnoea, a patient's oxygen

saturation will remain within normal limits for a period of time while supplemental oxygen administered. In other words, it may take minutes for a patient to desaturate. Therefore monitoring patient's oxygen saturations via pulse oximetry when supplemental oxygen is delivered, can be considered an insufficient practice, because despite respiratory issues, oxygen saturation parameters are likely to remain within normal values.

4.3 Limitations of this review

This systematic review had several limitations. A single reviewer screened the studies for eligibility against the inclusion criteria and extracted data from the included studies, increasing the potential for errors of omission. A further limitation is the sole inclusion of studies written in the English language. Furthermore, as additional information requested from Dr Mador (Mador et al., (2011), see Section 3.4.3), which sought to clarify aspects of the study results, patients' positions during the procedure and the oxygen administration during PSA, was not received, there is an acknowledged risk of bias in the reporting of this systematic review.

4.4 Implications for practice

The findings of this review are based on the results from an assessment of studies involving formally diagnosed OSA patients receiving PSA for GI endoscopy procedures. The small overall sample size and low number of reported adverse events in OSA patients undergoing GI endoscopies is not an adequate indicator of the safety of PSA for OSA patients undergoing other medical or diagnostic procedures where PSA is required. Therefore, definitive conclusions or recommendations for clinical practice are not possible.

4.5 Implications for research

This systematic review has demonstrated that only a small number of studies examining the association between adverse events and sedation in the OSA population have been published. Moreover, these studies only involved a small number of patients and the measurement of outcomes were not well defined. In addition, only studies conducted on patients undergoing endoscopic procedures were identified. In particular, studies investigating the association between

adverse events and the use of drugs in OSA patients would:

- be performed on patients undergoing diverse medical procedures (e.g. bone marrow biopsy, cardiac studies, etc.);
- use a standardised definition for the outcomes of interest such as hypo/hypertension, bradycardia, oxygen desaturation etc.;
- monitor and report airway obstruction, snoring and apnoea outcomes at least every 5 minutes;
- use capnography monitoring in addition to pulse oximetry monitoring for the early detection of respiratory events such as apnoea, hypopnoea and hypoventilation;
- report any airway support that might be required during the procedure (e.g. jaw support; use of guidel airways),
- report the use of antihypertensive and antiarrhythmic medication by patients. Highlight patients' baseline bradycardia and report prescribed beta-blockers;
- provide precise definitions of conditions, i.e., report the position of the patient during the procedure: supine, lateral; administration of supplemental oxygen administration;
- consider important confounding factors such as age, BMI, gender, as well as cardiovascular risk factors (e.g. diabetes, hypertension, ischaemic heart disease, hypercholesterolemia, smoking, alcohol intake); and
- perform subgroup analysis: separate OSA patients into mild, moderate and severe OSA.

To compare the adverse event rates in OSA and non-OSA patients, a well-designed matched case-control study is desirable. Ideally, the study would include a larger sample and both the cases and controls would comprise an equal number of patients. A homogenous group of patients with a confirmed diagnosis of OSA would be allocated to the OSA group (the cases), and similarly, a homogenous group of patients with a confirmed negative diagnosis of OSA would be allocated to the non-OSA group (the controls). Patients in the control group should have their non-OSA status confirmed using an overnight PSG. Identical nominated drug(s) would be administered to all patients to achieve sedation, and the incidence of cardiovascular and respiratory events would be compared between

the OSA and non-OSA groups. Participants selected for the control group would need to be matched as close as possible with members of the OSA group on confounding variables such as gender, age, BMI and family history, as well as for known cardiovascular risk factors such as hypertension, diabetes, smoking habits and alcohol intake. Furthermore, the OSA population could be divided into groups according to the apnoea-hypopnoea index (i.e. mild OSA, moderate OSA and severe OSA groups) so that a subgroup analysis and evaluation could be performed to determine if there was an association between adverse drug effects and severity of OSA. The study design would include standardised patient positioning during sedation administration.

4.6 Conclusions

The results of this systematic review with meta-analyses suggest there is no significant association between the diagnosis of OSA and PSA related complications. The limitations arising from the multiple gaps in reporting from across the included studies (notably, with regard to patient characteristics and outcome measurement) and the representativeness of the OSA population (OSA patients undergoing only endoscopic procedures) limit the extent to which the results can be interpreted and generalised. Although the included studies indicated there was no association between OSA and PSA, the reliability of the available data is too limited to allow for any definitive conclusions to be drawn.

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Appendix 1 Systematic review protocol

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Cardiopulmonary adverse events during procedural sedation in patients with obstructive sleep apnea: a systematic review protocol

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Review question/objective

This review aims to identify the type and incidence of cardiopulmonary adverse events during procedural sedation and analgesia (PSA) in patients with obstructive sleep apnea (OSA).

To achieve this objective, this review will address the following question:

What is the incidence of perioperative cardiopulmonary adverse events associated with PSA in patients with OSA? To address this question, this review will consider studies that compare outcomes in OSA patients with non-OSA patients,

as well as studies that report the adverse events of drugs used to induce PSA in OSA patients.

Background

Sleep is a natural state of rousable unconsciousness, which is marked by distinct phases of brainwave activity, and variations in muscle tone. Although muscle relaxation may be profound during sleep, in healthy individuals pharyngeal muscle tone maintains the airway structure, keeps the airway open and allows undisturbed breathing. In contrast, in patients with obstructive sleep apnea (OSA), the reduction of the tone of the pharyngeal muscles during sleep, causes the upper airway to narrow and makes the airway tissues less rigid. Decreased rigidity leads to upper airway collapse, typically at the site where the narrowing is at its greatest, this obstruction to airflow will remain present until sleep is interrupted, that is the individual awakes and muscle tone is restored.^{1, 2} Frequent arousals from sleep and disrupted sleep at night are responsible for the daytime lethargy and sleepiness in OSA patients.³ A typical feature of OSA is loud snoring due to the vibration of the soft tissues of the pharynx, soft palate and uvula while air is accelerating through these structures.⁴ Snoring is a manifestation of partial airway obstruction. Apnea occurs when partial airway obstruction transforms into complete airway obstruction.⁴ Loud snoring, by itself, is not confirmation of OSA. Recurrent pharyngeal collapse during sleep causes periods of reduction (hypopnea) or complete cessation (apnea) of airflow, causing a decrease in the level of oxyhemoglobin (measured by the percentage of haemoglobin saturated with oxygen) and potentially hypoxemia.⁵ Apnea can be defined as the cessation of oronasal airflow for ten seconds or longer.⁶ Hypopnea is a period of reduction of >30% of airflow for at least 10 seconds, and a >4% decrease in oxygen saturation.⁶

The severity of OSA is expressed as an apnea-hypopnea index (AHI), indicating the number of apnea or hypopnea events per hour.^{6, 7} The sum of apneas and hypopneas per hour of sleep is calculated and expressed as the AHI, giving a measure of the severity of the OSA (mild, 5-15 events per hour; moderate, 15-30 events per hour; and severe, >30 events per hour).⁶

Polysomnography (PSG) is considered to be the gold standard in diagnosis of OSA and is a comprehensive sleep study test, which involves an overnight stay in a sleep laboratory with multichannel monitoring. Monitoring and recording of physiological parameters undertaken during PSG includes brain functioning via electroencephalogram (EEG), eye movements via electro-oculogram (EOG), heart rate, oxygen saturation (oximetry), nasal airflow and intensity of snoring, chin and leg electro-myography and respiration with abdominal and thoracic respiratory effort.⁷

However, polysomnography is an expensive and time consuming test.⁶ To assist anesthesiologists with risk assessment for OSA in pre-operative settings, various screening questionnaires and clinical prediction models have been developed. The STOP-BANG questionnaire is a user-friendly, validated in surgical patients screening tool for severe OSA in the immediate preoperative period when OSA is highly suspected. It uses a linear scale and does not require further investigation.⁸ The patient answers “yes” or “no” to eight questions focused on the most commonly associated risk factors for OSA.

Patients with OSA are thought to be at increased risk for peri-operative respiratory or cardiac complications⁹⁻¹³ and, considering the multiple adverse health associations, OSA syndrome poses a potential concern for anesthesiologists, sedationists and proceduralists. Population-based large cohort epidemiological studies have established that there is a high prevalence of undiagnosed OSA in adults.¹⁴⁻¹⁷ Young et al. used Wisconsin Sleep Cohort Study data to estimate the prevalence of sleep disordered breathing in middle-aged, adult populations and found a prevalence of up to 5% of adults having undiagnosed OSA.^{7, 18} This observation was consistent across both Western and Asian populations. By contrast, other studies have found that the prevalence of OSA is higher in men (4%) than women (2%).^{7,19} OSA is strongly associated with obesity^{6,20} and an increasing age.^{18, 21, 22} Among obese patients (BMI>40 kg/m²), the prevalence of OSA is as high as 98%.²³ The prevalence of OSA is much higher (>50%) in patients with cardiac or metabolic disorders than in the general population.⁷ The prevalence of OSA in surgical patients is higher than in the general population,^{17, 24} and undiagnosed OSA is associated with increased perioperative morbidity and mortality.⁹

Anesthesia, when established, is a state of unrousable unconsciousness. The effects of anesthesia on airway muscular tone are similar to those described for OSA, so much so that the homogenous and profound loss of pharyngeal muscle tone may, if left untreated, result in asphyxia.^{3, 25, 26} Thus, maintenance of airway patency during sleep is a shared concern among anesthesiologists and sleep physicians, as both anesthesia and sleep predispose the upper airway to obstruction, mainly due to a loss of a wakeful pharyngeal tone.³ Eastwood et al²⁷ have demonstrated an association between increasing upper airway collapsibility, and increasing depth of sedation or anesthesia when using the anesthetic/hypnotic sedative drug propofol.

Procedural sedation and analgesia (PSA), with or without the addition of local anesthesia, may be administered to help patients tolerate painful, uncomfortable or otherwise distressing medical procedures. Unlike general anesthesia, patients undergoing PSA are required to maintain adequate control of airway and respiratory function without the assistance of airway devices or mechanical ventilation. Sedative and anesthetic medications produce a dose dependent depression of the arousal responses that usually protect against asphyxia.²⁸ As a result, patients with OSA receiving PSA are under increased risk of peri-operative complications. Gupta et al⁹ concluded that adverse postoperative outcomes occurred at a higher rate in patients with diagnosed OSA undergoing anesthesia for hip or knee replacement. However, there is limited evidence available supporting the increased risk of peri-operative side effects among the OSA population receiving PSA. This systematic review will focus on peri-operative cardiopulmonary complications in patients diagnosed with OSA following sedation and analgesia administration.

Procedural sedation is induced by the administration of drug(s) which induce analgesia, anxiolysis, amnesia, sleepiness and relaxation. Drugs used intravenously to induce PSA include opioids (e.g. fentanyl), benzodiazepines (e.g. midazolam, diazepam), propofol, ketamine and dexmedetomidine.^{29, 30} These may be used as a sole agent, or in various combinations. Examples of procedures that may be undertaken with intravenous PSA include diagnostic and therapeutic procedures such as colonoscopy, bone marrow biopsy, cardiac studies, endoscopy, bronchoscopy and dental procedures.³¹⁻³⁵

Known risks of procedural sedation include respiratory events, such as hypoventilation and progressive upper airways obstruction leading to apnea or hypopnea.³⁶ This may lead to hypoxemia and hypercarbia.^{36, 37} In non-anesthetized patients, hypoxemia and hypercarbia stimulate ventilation and increased respiratory effort breaks the cycle of airway obstruction.³⁶ Drug-induced sedation and analgesia can block the normal arousal and awakening in response to airway obstruction.³ In sedated patients normal arousal mechanisms can be suppressed when airway obstruction develops, leading to severe hypoxemia and hypercarbia, potentially predispose to hypo/hypertension, bradycardia/tachycardia and myocardial ischemia and ultimately to respiratory and cardiac arrest.^{3, 38, 39}

A preliminary literature search of EMBASE, MEDLINE, and the JBI and Cochrane libraries, has been undertaken. One systematic review and one meta-analysis were identified relating to the associations between sedation/anesthesia and obstructive sleep apnea.^{40, 41} Both reviews are specific to patients with OSA receiving anesthetic agents for surgical procedures (orthopaedic, general surgical abdominal, gynaecological, bariatric, neurosurgical, vascular, thoracic, ENT and other types of elective surgery).

The aim of this systematic review is to determine the relationship between cardiopulmonary adverse events in patients with and without OSA, undergoing diagnostic and/or therapeutic procedures (including, but not limited to, colonoscopy, bone marrow biopsy, cardiac studies, endoscopy, bronchoscopy or dental procedures) receiving midazolam and fentanyl PSA. Studies on patients undertaking surgical procedures under general anesthesia will be excluded from this review. A criteria for diagnosis of OSA includes formal sleep study, or those patients deemed at high risk of sleep apnea when assessed against the STOP-BANG criteria.⁴² This systematic review is needed, so the burden of morbidity and mortality among OSA population in settings where PSA is administered by both, anesthesiologists and non-anaesthesiologists can be determined.

Inclusion criteria

Types of participants

This review will consider studies of participants who are:

1. 18 years and older;
2. formally diagnosed with, or at risk for OSA (as determined by formal sleep study, or assessment against the STOP-BANG criteria); and
3. undergoing a diagnostic or therapeutic procedure with intravenous PSA.

Procedures that may be performed under PSA include, but are not limited to, bone marrow biopsy, colonoscopy, cardiac studies, endoscopy, bronchoscopy, minor plastic surgery, vascular stenting, and urological procedures.

Studies on OSA patients receiving sedation for drug induced sleep studies to examine upper airways, or receiving general anesthesia will be excluded from this review.

Types of intervention(s)/phenomena of interest

The incidence of perioperative cardiopulmonary adverse events associated with PSA:

1. In control (non-OSA) and OSA populations.
2. Evaluate studies involving (1) midazolam or fentanyl alone, or in combination, with or without local anesthesia; as compared to (2) PSA using propofol, with or without supplementary drugs including midazolam and fentanyl, with or without local anesthesia.

Studies in which propofol was the primary agent used for sedation, as assessed by the authors, will be allocated to the propofol group.

Types of outcomes

This review will consider studies that include the outcome measures (adverse events) as listed below. Criteria used to define these events may vary between published studies. Criteria used in each study will be reviewed and considered in an assessment of heterogeneity between studies.

Cardiovascular events:

- hyper/hypotension (20% or greater increase (hypertension) or decrease (hypotension) in the pre-procedural blood pressure value or, any single systolic blood pressure reading below 80 mmHg or above 160 mmHg)
- significant arrhythmias (e.g. AV heart block, ventricular tachycardia, atrial fibrillation)
- brady/tachycardia (e.g. < 50 beats per minute, or ≥ 120 beats per minute)
- chest pain
- cardiac arrest
- heart failure

Pulmonary events:

- loss of airway patency
- hypoventilation (e.g. respiratory rate ≤ 8 breaths per minute)
- oxygen desaturation (e.g. saturation of oxygen, sPO₂, $\leq 92\%$).
- laryngospasm
- bronchospasm
- aspiration

Mortality and morbidity

Types of studies

This review will consider both experimental and epidemiological study designs including randomized controlled trials, non-randomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies and analytical cross sectional studies for inclusion.

Search strategy

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will

then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English will be considered for inclusion in this review. Obstructive sleep apnea was first described in the literature more than 100 years ago. The disorder was rediscovered, and recognised as a medical condition and described in the medical literature only in 1965. Studies published from 1965 until present time (2013), which meet the inclusion criteria for this review, will be included in the search.

The databases to be searched include:

PubMed, EMBASE, CINAHL, Cochrane Central Trials Register and Scopus.

The search for unpublished studies will include:

Current Controlled Trials, ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry (anzctr.org.au), and ProQuest Dissertations and Theses.

Initial keywords to be used will be:

Obstructive sleep apnea, sleep apnea syndrome, sleep apnea, sleep disordered breathing, sleep hypopnea, OSA, OSAH, apnea hypopnea syndrome, hypersomnia with periodic respirations, upper airway, upper airway resistance, upper airway obstruction;

Short acting anesthesia, sedation, conscious sedation, propofol, diprivan, fentanyl, midazolam neuroleptanalgesia, anesthesia and analgesia, anesthetic

Safety, complication(s), morbidity, mortality, adverse events, postoperative complications.

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardised critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MASARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data collection

Data will be extracted from papers included in the review using the standardised data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Quantitative data will, where possible be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square and also examined via subgroup analyses isolating the different means of diagnosing OSA patients and the severity of OSA, where possible. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Conflicts of interest

None

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Appendix 2 STOP-BANG questionnaire

1. Snoring: Do you snore loudly (loud enough to be heard through closed doors)?

Yes No

2. Tired: Do you often feel tired, fatigued, or sleepy during daytime?

Yes No

3. Observed: Has anyone observed you stop breathing during your sleep?

Yes No

4. Blood pressure: Do you have or are you being treated for high blood pressure?

Yes No

5. BMI: BMI more than 35 kg m^{-2} ?

Yes No

6. Age: Age over 50 yr. old?

Yes No

7. Neck circumference: Neck circumference $>40 \text{ cm}$?

Yes No

8. Gender: Male?

Yes No

High risk of OSA: Yes to ≥ 3 questions

Low risk of OSA: Yes to < 3 questions

Questionnaire reproduced from Chung, F., Yegneswaran, B., Liao, P., Chung, S. A., Vairavanathan, S., Islam, S., Khajehdehi, A., Shapiro, C. M.. *STOP questionnaire: a tool to screen patients for obstructive sleep apnea*. *Anesthesiology*.2008; 108(5): 812-21.

Appendix 3 Search strategy

PubMed Search (Conducted 30/03/2014. Auto run of search continued until May 2015. Search completed on 15th of May 2015)

#1 Sleep apnea syndromes[mh] OR sleep apnoea syndromes[mh] OR Sleep apnea syndrome[mh] OR sleep apnoea syndrome[mh] OR sleep apnea*[tw] OR sleep apnoea*[tw] OR sleep hypopnoea*[tw] OR sleep hypopnea*[tw] OR OSA[tiab] OR OSAH[tiab] OR OSAHS[tiab] OR Apnoea hypopnoea syndrome*[tw] OR Apnea hypopnea syndrome*[tw] OR sleep disordered breathing[tw] OR Hypersomnia with Periodic Respiration[tiab] OR upper airway resistance[tw] OR upper airway obstruction[tw] OR nocturnal apnea[tw] OR nocturnal apnoea[tw]

#2 Short acting anesthesia[tw] OR short acting anaesthesia[tw] OR Short acting anesthetic*[tw] OR short acting anaesthetic*[tw] OR conscious sedation[tw] OR conscious sedation[mh] OR sedation[tw] OR anesthesia and analgesia[mh:noexp] OR anesthesia[tw] OR anaesthesia[tw] OR analgesia[tw] OR anaesthetic*[tw] OR anesthetic*[tw] OR fentanyl[tw] OR phentanyl[tw] OR fentanest[tw] OR sublimase[tw] OR fentora[tw] OR R-4263[tw] OR duragesic[tw] OR fetnanyl[tw] OR instanyl[tw] OR ionsys[tw] OR lazanda[tw] OR leptanal[tw] OR onsolis[tw] OR pecfent[tw] OR rapinyl[tw] OR recuvyra[tw] OR subsys[tw] OR tanyl[tw] OR trnsfenta[tw] OR midazolam[tw] OR versed[tw] OR dormicum[tw] OR Ro-213981[tw] OR Ro-213981003[tw] OR hypnovel[tw] OR hypnoval[tw] OR hypnoyvel[tw] OR ipnovel[tw] OR midacum[tw] OR midazo[tw] OR midazol[tw] OR midolam[tw] OR miloz[tw] OR buccolam[tw] OR dalam[tw] OR doricum[tw] OR dormonid[tw] OR fortanest[tw] OR fulsed[tw] OR propofol[tw] OR diprivan[tw] OR aneprol[tw] OR crytol[tw] OR diisoprofol[tw] OR disoprivan[tw] OR disoprofol[tw] OR fresofol[tw] OR gobbifol[tw] OR ici 35868[tw] OR pofol[tw] OR propocam[tw] OR propofol-lipuro[tw] OR rapinovel[tw] OR recofol[tw] OR safol[tw]

#3 #1 AND #2

Limits: English language

CINAHL (EBSCOHost) Search (Conducted 30/03/2014. Auto run of search continued until May 2015. Search completed on 15th of May 2015)

S1 MH Sleep Apnea Syndromes+ OR AB "Sleep Apnea Syndromes" OR TI "Sleep Apnea Syndromes" OR MH sleep apnea, obstructive+ OR AB "obstructive sleep apnea" OR TI "obstructive sleep apnea" OR MH "sleep apnea*" OR AB "sleep apnea*" OR TI "sleep apnea*" OR MH "sleep hypopnea*" OR AB "sleep hypopnea*" OR TI "sleep hypopnea*" OR MH "OSA" OR AB "OSA" OR TI "OSA" OR MH "OSAHS" OR AB "OSAHS" OR TI "OSAHS" OR MH Apnea hypopnea syndrome* OR AB "Apnea hypopnea syndrome*" OR TI "Apnea hypopnea syndrome*" OR MH sleep disordered breathing OR AB "sleep disordered breathing" OR TI "sleep disordered breathing" OR MH Hypersomnia N3 Respiration OR AB "Hypersomnia N3 Respiration" OR TI "Hypersomnia N3 Respiration*" OR MH upper airway resistance OR AB "upper airway resistance" OR TI "upper airway resistance" OR MH upper airway obstruction* OR AB "upper airway obstruction*" OR TI "upper airway obstruction*" OR MH Sleep Apnoea Syndromes+ OR AB "Sleep Apnoea Syndromes" OR TI "Sleep Apnoea Syndromes" OR MH sleep apnoea, obstructive+ OR AB "obstructive sleep apnoea" OR TI "obstructive sleep apnoea" OR MH "sleep apnoea*" OR AB "sleep apnoea*" OR TI "sleep apnoea*" OR MH "sleep hypopnoea*" OR AB "sleep hypopnoea*" OR TI "sleep hypopnoea*" OR MH Apnoea hypopnoea syndrome* OR AB "Apnoea hypopnoea syndrome*" OR TI "Apnoea hypopnoea syndrome*" OR MH "obstructive sleep apnea hypopnea syndrome" OR AB "obstructive sleep apnea hypopnea syndrome" OR TI "obstructive sleep apnea hypopnea syndrome" OR MH "obstructive sleep apnoea hypopnoea syndrome" OR AB "obstructive sleep apnoea hypopnoea syndrome" OR TI "obstructive sleep apnoea hypopnoea syndrome"

S2 MH "Hypnotics and Sedatives+" OR AB "Hypnotics and Sedatives" OR "Hypnotics and Sedatives" OR MH "Conscious sedation"+ OR AB "Conscious sedation" OR TI "Conscious sedation" Or MH analgesia OR AB analgesia OR TI analgesia OR MH short acting anesthetic*+ OR AB "short acting anesthetic*" OR TI "short acting anesthetic*" OR MH short acting anaesthetic*+ OR AB "short acting anaesthetic*" OR TI "short acting anaesthetic*" OR MH short acting anesthesia+ OR AB "short acting anesthesia" OR TI "short acting anesthesia" OR

MH short acting anaesthesia+ OR AB "short acting anaesthesia" OR TI "short acting anesthesia" OR MH "anesthesia and analgesia" OR AB "anesthesia and analgesia" OR TI "anesthesia and analgesia" OR MH "anaesthesia and analgesia" OR AB "anaesthesia and analgesia" OR TI "anaesthesia and analgesia" OR MH Midazolam+ OR AB midazolam OR TI midazolam OR MH hypnoval OR AB hypnoval OR TI Hypnoval OR MH hypnovel OR AB hypnovel OR TI hypnovel OR MH versed OR AB versed OR TI versed OR MH dormicum OR AB dormicum OR TI dormicum OR HM "Ro-213981" OR AB "Ro-213981" OR TI "Ro-213981" OR MH Fentanyl+ OR AB fentanyl OR TI fentanyl OR MH fentanest OR AB fentanest OR TI fentanest OR MH sublimase OR AB sublimase OR TI sublimase OR MH fentora OR AB fentora OR TI fentora OR MH "R-4263" OR AB "R-4263" OR TI "R-4263" OR MH phentanyl OR AB phentanyl OR TI phentanyl OR MH "Propofol" OR AB propofol OR TI propofol OR MH diprivan OR AB diprivan OR TI diprivan) OR MH "Hypnotics and Sedatives+" OR AB "Hypnotics and Sedatives" OR "Hypnotics and Sedatives" OR MH "Conscious sedation"+ OR AB "Conscious sedation" OR TI "Conscious sedation" Or MH analgesia OR AB analgesia OR TI analgesia OR MH short acting anesthetic*+ OR AB "short acting anesthetic*" OR TI "short acting anesthetic*" OR MH short acting anaesthetic*+ OR AB "short acting anaesthetic*" OR TI "short acting anaesthetic*" OR MH short acting anesthesia+ OR AB "short acting anesthesia" OR TI "short acting anesthesia" OR MH short acting anaesthesia+ OR AB "short acting anaesthesia" OR TI "short acting anaesthesia" OR MH "anesthesia and analgesia" OR AB "anesthesia and analgesia" OR TI "anesthesia and analgesia" OR MH "anaesthesia and analgesia" OR AB "anaesthesia and analgesia" OR TI "anaesthesia and analgesia" OR MH Midazolam+ OR AB midazolam OR TI midazolam OR MH hypnoval OR AB hypnoval OR TI Hypnoval OR MH hypnovel OR AB hypnovel OR TI hypnovel OR MH versed OR AB versed OR TI versed OR MH dormicum OR AB dormicum OR TI dormicum OR HM "Ro-213981" OR AB "Ro-213981" OR TI "Ro-213981" OR MH Fentanyl+ OR AB fentanyl OR TI fentanyl OR MH fentanest OR AB fentanest OR TI fentanest OR MH sublimase OR AB sublimase OR TI sublimase OR MH fentora OR AB fentora OR TI fentora OR MH "R-4263" OR AB "R-4263" OR TI "R-4263" OR MH phentanyl OR AB phentanyl OR TI phentanyl

OR MH "Propofol" OR AB propofol OR TI propofol OR MH diprivan OR AB diprivan OR TI diprivan

S3 S1 AND S2

Limiters/Expanders: Search modes - Find all my search terms

EMBASE (Ovid) Search (Conducted 30/03/2014. Auto run of search continued until May 2015. Search completed on 15th of May 2015)

#1 'sleep disordered breathing'/syn OR 'osa':ab,ti OR 'osah':ab,ti OR 'osahs':ab,ti OR 'sleep apnea syndromes':ab,ti OR 'sleep apnoea syndromes':ab,ti OR 'sleep apnea syndrome':ab,ti OR 'sleep apnoea syndrome':ab,ti OR 'sleep apnea':ab,ti OR 'sleep apnoea':ab,ti OR 'sleep hypopnoea':ab,ti OR 'sleep hypopnea':ab,ti OR 'apnoea hypopnoea syndrome':ab,ti OR 'apnea hypopnea syndrome':ab,ti OR 'sleep disordered breathing':ab,ti OR 'hypersomnia with periodic respiration':ab,ti OR 'upper airway resistance':ab,ti OR 'upper airway obstruction':ab,ti OR 'nocturnal apnea':ab,ti OR 'nocturnal apnoea':ab,ti

#2 'short acting anesthesia':ab,ti OR 'short acting anaesthesia':ab,ti OR 'short acting anesthetic':ab,ti OR 'short acting anesthetics':ab,ti OR 'short acting anaesthetic':ab,ti OR 'short acting anaesthetics':ab,ti OR 'anesthesia and analgesia':ab,ti OR 'anaesthesia and analgesia':ab,ti OR 'sedation'/exp OR 'deep sedation':ab,ti OR 'conscious sedation':ab,ti OR 'moderate sedation':ab,ti OR 'analgesia'/exp OR 'hypnotic sedative agent'/exp OR 'propofol'/syn OR 'midazolam'/syn OR 'fentanyl'/syn

#3 #1 AND #2

Limits: English

Scopus Search (Conducted 30/03/2014. Auto run of search continued until May 2015. Search completed on 15th of May 2015)

#1 (TITLE-ABS-KEY("Sleep apnea syndromes" OR "sleep apnoea syndromes" OR "Sleep apnea syndrome" OR "sleep apnoea syndrome" OR "sleep apnea" OR "sleep apnoea" OR "sleep hypopnoea" OR "sleep hypopnea" OR "OSA" OR "OSAH" OR "OSAHS" OR "Apnoea hypopnoea syndrome" OR "Apnea hypopnea syndrome" OR "sleep disordered breathing" OR "Hypersomnia with Periodic Respiration" OR "upper airway resistance" OR "upper airway obstruction" OR "nocturnal apnea" OR "nocturnal apnoea"))

#2 (TITLE-ABS-KEY("sedation" OR "moderate sedation" OR "conscious sedation" OR "deep sedation" OR "short acting anaesthesia" OR "short acting anesthesia" OR "short acting anaesthetic" OR "short acting anesthetic" OR "short acting anaesthetics" OR "short acting anesthetics" OR "anaesthesia and analgesia" OR "anesthesia and analgesia" OR "anaesthesia and analgesia" OR "analgesia" OR "anesthetic" OR "anesthetics" OR "anaesthetic" OR "anaesthetics" OR "fentanyl" OR "phentanyl" OR "fentanest" OR "sublimase" OR "fentora" OR "R-4263" OR "duragesic" OR "fentamyl" OR "fentanil" OR "instanyl" OR "ionsys" OR "lazanda" OR "leptanal" OR "onsolis" OR "pecfent" OR "rapinyl" OR "recuvyra" OR "subsys" OR "tanyl" OR "trnsfenta" OR "midazolam" OR "versed" OR "dormicum" OR "Ro-213981" OR "Ro-213981003" OR "hypnovel" OR "hypnoval" OR "hypnoyvel" OR "ipnovel" OR "midacum" OR "midazo" OR "midazol" OR "midolam" OR "miloz" OR "buccolam" OR "dalam" OR "doricum" OR "dormonid" OR "fortanest" OR "fulsed" OR "propofol" OR "diprivan" OR "aneprol" OR "cryotol" OR "diisoprofol" OR "disoprivan" OR "disoprofol" OR "fresofol" OR "gobbifol" OR "ici 35868" OR "pofol" OR "propocam" OR "propofol-lipuro" OR "rapinovet" OR "recofol" OR "safol"))

#3 #1 AND #2

Limits: English language

Appendix 4 Adapted Joanna Briggs Institute Meta Analysis Statistics Assessment and Review Instrument (JBI-MAStARI).

(Critical appraisal tool for cohort studies (JBI Reviewers Handbook, 2014))

1. *Is the sample representative of patients in the population as a whole?*

YES	<p>Authors described obstructive sleep apnea (OSA) population Is the sample of OSA population in the study is truly representing OSA population as a whole? Is the study investigating OSA population undertaking procedure under sedation? How OSA population was selected? E.g. patients from the sleep study centre were selected and then, OSA and non-OSA groups were formed, and then the procedure under sedation was undertaken. Authors described whether their OSA group has got a confirmed OSA diagnosis. For example, the following methods could be used to diagnose OSA: i) Overnight polysomnography ii) STOP-BANG questionnaire iii) Portable monitoring Authors reported in their study that CPAP therapy used/not used by the patients in OSA group Population sample sizes were given. Were the numbers adequate to make the study sufficiently powerful to capture less common complications? Were OSA and control matched in size?</p>
NO	<p>No mention of how OSA population was selected OSA population outlined in the study is not representing OSA population as a whole Methods used to diagnose OSA were not described by the authors Small OSA population size</p>
Unclear	Unclear descriptions of any/all the above

Note:

2. *Are the patients at a similar point in the course of their condition/illness?*

YES	<p>For example, OSA patients were divided into subgroups according to apnea-hypopnea index (AHI) (Reference 6,7 in my Protocol), e.g.: Mild OSA (5-15 of apneas or hypopneas (events) per hour of sleep) Moderate OSA (15-30 events per hour of sleep) Severe OSA (>30 events per hour of sleep) Authors described parameters they used when selecting patients for their OSA group (e.g. patients with only moderate and severe OSA were included in their study; whether only the patients using CPAP/Bi-PAP machine during sleep at night were included in their study?)</p>
NO	Authors did not divide OSA group into subgroups according to AHI

	Authors created only two groups: OSA and control group for comparison
Unclear	Unclear descriptions of any/all the above

NOTE:

3. *Has bias been minimized in relation to selection of cases and controls?*

YES	<p>Was the control group screened? How the control group was screened (e.g. by the results of sleep study - negative sleep study; or questionnaire used: STOP-BANG or Berlin questionnaire; any other methods used)?</p> <p>The numbers of patients at each stage of the study were reported</p> <p>Exclusion criteria in selecting cases for study was defined</p> <p>The period when observations were taken is defined (e.g. measurements are taken in a perioperative period; patients met the discharge criteria from recovery room)</p> <p>Confounding factors were listed by the authors</p>
NO	<p>No description of how control group was selected</p> <p>No mention how the control group was screened</p> <p>The period when observations were taken is not defined</p> <p>No confounding factors were listed by the authors</p> <p>Exclusion criteria was not defined</p>
Unclear	Details of all of the above are unclear

4. *Are confounding factors identified and strategies to deal with them stated?*

YES	<p>Following key confounders were listed:</p> <ul style="list-style-type: none"> Age Sex Weight BMI Smoking Hypertension Diabetes <p>Above confounders were described and adjusted for in the analyses</p> <p>Any remaining confounders (e.g. ASA classification, neck circumference; alcohol intake; family history, race) described and included in the study</p> <p>Patients undertaken diagnostic or/and therapeutic procedures such as endoscopy (esophagogastroduodenoscopy [EGD]), colonoscopy, bronchoscopy, cardiac studies, bone marrow biopsy; any other procedures suitable to be undertaken under sedation, as outlined in my Protocol. Procedures, where the degree of stimulation during the procedure would be similar, so, the level of analgesia and sedation requirements would be similar. Description of the procedure is an advantage.</p> <p>Authors documented patients position during the procedure (supine,</p>
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	<p>lateral or prone)</p> <p>Details of intervention (sedation administration) were provided by the authors</p> <p>Dose and description of how the drug was administered (e.g. mg per kg of patient's weight; time interval between given doses, a bolus dose or infusion, etc)</p> <p>Level of sedation described by the authors (e.g. moderate, deep)</p> <p>As listed in Protocol, drugs fentanyl, midazolam, or propofol administered intravenously alone, or in combination were used for sedation of the patients</p> <p>Authors reported in the study who was administering sedation and analgesia for the specified procedure (e.g. proceduralist, anaesthesiologist, nurse) is an advantage</p>
NO	<p>Only some of the key confounders were listed</p> <p>No mention of confounders</p> <p>No description of intervention (doses and how medications were administered) was given by the authors</p> <p>No mention of how patient was positioned for procedure</p> <p>No mention of who was administering sedation</p>
Unclear	<p>Explanation of confounders unclear</p>

Note: The listed above key confounders are imperative. The study, where the **key** confounders (at least some of them) were not listed and /or not adjusted for the analysis could not be included in my systematic review

5. Are outcomes assessed using objective criteria?

YES	<p>Description of how data was collected</p> <p>For measurement of cardiovascular and respiratory outcomes authors described methods used to detect the adverse events:</p> <p>Instruments such as an automatic blood pressure or manual blood pressure machine was used to monitor patients' blood pressure (BP)</p> <p>Continuous cardiac monitoring via electrocardiographic leads attached to the patients skin was used for monitoring patients heart rate and rhythm, and consequently for monitoring of cardiac arrhythmias</p> <p>Patients' assessment was performed continuously and authors stated if patients complained on chest pain.</p> <p>At a minimum, continuous pulse-oximetry used to detect oxygen desaturation</p> <p>Any other adverse events were recorded and any interventions performed were documented</p> <p>Criteria used to define the above events may vary between published studies</p>
NO	<p>Adverse events were not defined by the authors</p> <p>No documentation on how the measurements were taken</p>
Unclear	<p>Unclear descriptions of outcomes and how the measurements were taken</p>

6. *Is follow-up carried out over a sufficient time period?*

YES	Post-procedural observations and /or complications are described by the authors. It is possible that a patient who underwent a medical/surgical procedure would develop a delayed response following that procedure. For example, in Australia, any death of a person within 24 hours post medical or surgical procedure must be reported to the Coroner Office for investigation. So, it is appropriate to expect, that a documentation of the patient developing complications or returning to the health facility during next twenty four hours post-procedure would be reflected in the study.
NO	Only the measurements and observations that are taken during perioperative period; and/or patients met the discharge criteria from the recovery are documented No information on follow up of the patients who underwent surgical/medical procedure
Unclear	Details of all of the above are unclear

7. *Are the outcomes of people who withdrew described and included in the analysis?(Prospective studies only)*

YES	All patients withdrew from the study were reported and the reasons for withdrawal described The measured outcomes of the withdrawn patients included in the final calculations
NO	No explanation of why patients withdrew from the study were provided by the authors
Unclear	Unclear explanation of why patients withdrew from the study Withdrawal patients incompletely described
N/A	Retrospective study

8. Are outcomes measured in a reliable way?

YES	<p>For measurement and monitoring of respiratory events such as oxygen desaturation, authors, for example used a continuous pulse-oximetry. In the event of loss of airway patency, authors described the techniques and equipment that was used to restore airway patency. Respiratory rate (e.g.) below eight breath per minute was used as an indication of hypoventilation. For example, chest auscultation was performed to detect bronchospasm. Authors documented their action during the events of laryngospasm or aspiration.</p> <p>For monitoring of airway obstruction, hypoventilation and apnoea, a capnography monitoring is utilised by the authors</p> <p>The definitions of the outcomes of interest are reported</p> <p>The frequency of measurements is reported</p>
NO	<p>No information was given by the authors on what instruments were used to measure of (e.g.) blood pressure or oxygen saturations</p> <p>No information on capnography monitoring</p> <p>No information on monitoring of airway obstruction, hypoventilation and apnoea</p> <p>Inadequate reporting of frequency of oxygen saturation, blood pressure and heart rate</p> <p>Inadequate reporting of definitions of outcomes of interest</p>
Unclear	<p>Not enough, or partial information was given to determine how the outcomes were measured</p> <p>Authors reported that “standard monitoring” was used to record vital signs</p>

9. Was appropriate statistical analysis used?

YES	<p>Appropriate statistical methods used, described and reported.</p> <p>Methods for addressing confounding factors included in the study.</p>
NO	<p>Statistical methods not described, or inappropriate methods used</p> <p>Missing patients data not reported</p>
Unclear	<p>Statistical methods unclear</p>

Appendix 5 Data extraction template

	Description
Author, year of publication	
Study design	
Aim of study	

Population and setting

	Description as stated in the study
Setting	
Population of interest	
Total number of patients	
Number of patients with OSA	
Number patients without OSA (control)	
Patient characteristics and baseline clinical data	
Method of analysis used to detect OSA	
Methods of analysis to confirm absence of OSA (control group)	

Intervention

	Drugs used for sedation
Sedation administration	

Outcomes

	Description as stated in the study
Reported outcomes	
Description of outcomes as stated by the authors	

Results

Outcomes and definition of outcomes by study authors	Number of events in OSA group	Number of events in non-OSA group	P value
Hypotension			
Hypertension			
Bradycardia			
Tachycardia			
Oxygen desaturation			
Apnoea/snoring			
Hypoventilation			
Complications requiring intervention			

Appendix 6 List of excluded records

(Endnote 16.09.14), updated in September 2015 (2 citations added to the list):

Jackson, D., et al., *Interscalene nerve block in patients with obstructive sleep apnea undergoing ambulatory shoulder arthroscopy*. Regional Anesthesia and Pain Medicine, 2013. **38**(4).

Reason for exclusion: A conference abstract. No full paper could be found

Kawa, C.B., et al., *A retrospective study of the safety of nurse administered propofol sedation (NAPS) in patients with obstructive sleep apnea (OSA) undergoing routine endoscopy*. Gastrointestinal Endoscopy, 2010. **71**(5): p. AB251.

Reason for exclusion: A conference abstract. No full paper could be found

Andrade, C., et al., *Evaluation of the safety of conscious sedation and gastrointestinal endoscopy in the veteran population with sleep apnea*. American Journal of Gastroenterology, 2013. **108**: p. S480.

Reason for exclusion: A conference abstract. The conference abstract was not included, because a full paper was published and that study was included in the review.

Cote, G.A., et al., *Prevalence of obstructive sleep apnea among patients undergoing advanced endoscopic procedures using crna-administered propofol for sedation: Use of a bedside screening instrument to predict sedation-related complications*. Gastroenterology, 2010. **138**(5): p. S640.

Reason for exclusion: A conference abstract. A full paper located. Study on high risk of OSA patients. Patients with confirmed OSA not included in this study.

Gill, J.A., et al., *Safety of conscious sedation during endoscopy for patients with obstructive sleep apnea versus controls in a veteran population*. Gastrointestinal Endoscopy, 2010. **71**(5): p. AB218.

Reason for exclusion: A conference abstract. The conference abstract was not included, because a full paper was published and that study was included in the review.

Kaw et al., 2012 Meta-analysis of the associations between OSA and post-operative outcome. British Journal of Anaesthesia, 2012. 109 (6): 897–906.

Reason for exclusion: A systematic review of peri-operative sedatives and anaesthetics in surgical patients with OSA.

Gaddam S., S.K.Gunukula, M.J.Mador, *Post-operative outcomes in adult obstructive sleep apnea patients undergoing non-upper airway surgery: a systematic review and meta-nalysis*. Sleep Breath, 2014. 18:615-633.

Reason for exclusion: A systematic review of peri-operative sedatives and anaesthetics in surgical patients with OSA.

Gaddam S., S.K. Gunukula, M.J. Mador *Post-gastrointestinal endoscopy complications in patients with obstructive sleep apnea or at high risk for sleep apnea: A systematic review and meta-analysis.* Sleep Breath, 2015. Springer, published online.

Reason for exclusion: A systematic review.

Ankichetty, S., J. Wong, and F. Chung, *A systematic review of the effects of sedatives and anesthetics in patients with obstructive sleep apnea.* Journal of Anaesthesiology Clinical Pharmacology, 2011. **27**(4): p. 447-458.

Reason for exclusion: A systematic review of perioperative sedatives and anaesthetics in surgical patients with OSA.

Berend, K.R., et al., *Prevalence and management of obstructive sleep apnea in patients undergoing total joint arthroplasty.* Journal of Arthroplasty, 2010. **25**(SUPPL. 6): p. 54-57.

Reason for exclusion: Wrong intervention. The purpose of this retrospective study is to determine (1) prevalence of OSA in patients undertaking total joint arthroplasty (TJA) and how OSA correlates with perioperative complications for the above procedure; and (2) the safety and effectiveness of intrathecal narcotics (IN) duramorphine and bupivacaine anesthesia and local anaesthetic for perioperative analgesia and anaesthesia in OSA patients undergoing TJA. It is quite common to add intravenous sedation or give general anaesthetic following IN anaesthesia for the procedure that is mentioned above. It is more likely, that the patients received sedation or general anaesthesia for TJA, but authors did not describe it. Authors did not mention if general anaesthesia or sedation was used in addition to IN anaesthesia.

Bolden, N., C.E. Smith, and D. Auckley, *Avoiding adverse outcomes in patients with obstructive sleep apnea (OSA): development and implementation of a perioperative OSA protocol.* Journal of Clinical Anesthesia, 2009. **21**(4): p. 286-293.

Reason for exclusion: Not a study; case reports.

Bolden, N., et al., *Perioperative complications during use of an obstructive sleep apnea protocol following surgery and anesthesia.* Anesth Analg, 2007. **105**(6): p. 1869-70.

Reason for exclusion: Not a study; letter to the editor.

Bose, S., *Obstructive sleep apnea and perioperative complications.* Chest, 2008. **134**(4): p. 890-1.

Reason for exclusion: Not a study; letter to the editor.

Bryson GL, Gomez CP, Jee RM, Blackburn J, Taljaard M, Forster AJ. *Unplanned admission after day surgery: A historical cohort study in patients with obstructive sleep apnea.* Can J/J Can Anesth (2012) 59:842-851.

Reason for exclusion: Wrong intervention. The purpose of this study is to estimate the rates of unplanned hospital admission following ambulatory surgery in patients diagnosed with OSA and treated with positive airway pressure in patients without OSA. This study involves patients receiving general anaesthesia for ambulatory surgery including orthopaedic surgery, laparoscopic surgery, and surgery of the upper abdomen. Authors excluded procedures performed with monitored anaesthesia care such as gastrointestinal endoscopy and ophthalmological surgery.

Campo, F.D. and C. Zamarron, *Gastrointestinal endoscopy in patients with obstructive sleep apnea syndrome*. *Sleep and Breathing*, 2012. **16**(3): p. 591-592.

Reason for exclusion: Not a study; letter to the editor.

Chau, E.H.L., et al., *Obesity hypoventilation syndrome: A review of epidemiology, pathophysiology, and perioperative considerations*. *Anesthesiology*, 2012. **117**(1): p. 188-205.

Reason for exclusion: Author manuscript; review paper.

Chung F., *It may be unsafe for patients with untreated severe OSA requiring postoperative narcotic to undergo ambulatory surgery*. *Journal of Clinical Sleep Medicine*, Vol 7, No 1, 2011

Reason for exclusion: Not a study; letter to the editor.

CORSO R., PIRACCINI E., AGNOLETTI V., LIPPI M., BUCCIOLI M., NEGRO A., GAMBALE G., RICCI E. *Clinical use of the STOP-BANG questionnaire in patients undergoing sedation for endoscopic procedures* MINERVA ANESTESIOLOGICA, 2012. Vol. 78 - No. 1

Reason for exclusion: Wrong population; study on high risk of OSA patients.

Cote, G.A., et al., *A screening instrument for sleep apnea predicts airway maneuvers in patients undergoing advanced endoscopic procedures*. *Clinical Gastroenterology and Hepatology*, 2010. **8**(8): p. 660-665.e1.

Reason for exclusion: Wrong population: study on high risk of OSA patients. STOP-BANG tool used preoperatively and was used as a predicting factor for airway manoeuvres. According to the STOP-BANG assessment, selected for this study patients are at high risk for OSA. In fact, confirmed OSA patients were excluded from this study.

Dakin, J. and M. Margaron, *Sleep-disordered breathing and anaesthesia in the morbidly obese*. *Current Anaesthesia and Critical Care*, 2010. **21**(1): p. 24-30.

Reason for exclusion: Not a study; discussion paper.

Daley, M.D., P.H. Norman, and L.A. Coveler, *Additional safety issues cited for sleep apnea cases [3]*. Journal of Clinical Monitoring and Computing, 1998. **14**(3): p. 213-214.

Reason for exclusion: Not a study; letter to the editor.

Davis, B. and J.R. Brady, *Safety and efficacy of propofol-only sedation in oral and maxillofacial surgery-pilot study*. Journal of Oral and Maxillofacial Surgery, 2013. **71**(9): p. e40-e41.

Reason for exclusion: Wrong population; study on non-OSA patients.

D'Apuzzo MR, Browne JA. *Obstructive sleep apnea as a risk factor for postoperative complications after revision joint arthroplasty*. The Journal of Arthroplasty. 2012;27(8) Suppl.1

Reason for exclusion: Wrong study design; no primary data.

Study on association of OSA and morbidity after hip or knee revision arthroplasty. The nationwide (United States) inpatient sample was used to identify patients who underwent total hip revision and revision of knee arthroplasty.

Dhanda Patil, R. and Y.J. Patil, *Perioperative management of obstructive sleep apnea: a survey of Veterans Affairs health care providers*. Otolaryngol Head Neck Surg, 2012. **146**(1): p. 156-61.

Reason for exclusion: Wrong study design. Study on pre-operative screening for OSA and post-operative management care of veteran patients.

Efken C, Bitter T, Prib N, Horstkotte D, Oldeburg O. *Obstructive sleep apnoea: longer respiratory event lengths in patients with heart failure*. European Respiratory Journal June 1, 2013.41(6):1340-1346.

Reason for exclusion: Wrong study design. This study investigates the influence of heart failure on OSA. This study is comparing two groups of patients with OSA: OSA group with heart failure and OSA group without heart failure.

Esclamado, R.M., et al., *Perioperative complications and risk factors in the surgical treatment of obstructive sleep apnea syndrome*. Laryngoscope, 1989. **99**(11): p. 1125-9.

Reason for exclusion: Wrong study design: study on surgical treatment of OSA.

Eshleman, M.R., *Obstructive sleep apnea and ambulatory surgery*. J Clin Monit Comput, 1998. **14**(3): p. 217.

Reason for exclusion: Not a study; letter to the editor.

Goudra, B.G., et al., *Significantly reduced hypoxemic events in morbidly obese patients undergoing gastrointestinal endoscopy: Predictors and practice effect*. J Anaesthesiol Clin Pharmacol, 2014. **30**(1): p. 71-7.

Reason for exclusion: Wrong study design. Study on in morbidly obese patients. The study found that frequency of desaturation episodes showed statistically significant relation to previous history of obstructive sleep apnoea.

Griffin JW, Novicoff WM, Browne JA, Brockmeier SF. *Obstructive sleep apnea as a risk factor after shoulder arthroplasty*. Journal of Shoulder and Elbow Surgery (2013) 22, e6-e9.

Reason for exclusion: Wrong study design: no primary data available. A large-scale database analysis. The aim of this study was to determine in-hospital complications, in-hospital mortality, lengths of stay and postoperative charges in patients with OSA compared to non-OSA patients undertaking shoulder arthroplasty.

Jones, R., *Endoscopy: Snoring while under conscious sedation during colonoscopy is linked to obstructive sleep apnea*. Nature Reviews Gastroenterology and Hepatology, 2010. 7(8): p. 418.

Reason for exclusion: Not a study; letter to the editor.

Junna, M.R., B.J. Selim, and T.I. Morgenthaler, *Medical sedation and sleep apnea*. Sleep Medicine Clinics, 2013. 8(1): p. 43-58.

Reason for exclusion: Not a study; review paper on the effects of hypno-sedatives and opioids on breathing control.

Kabeli, C., *Obstructive sleep apnea and modifications in sedation*. Crit Care Nurs Clin North Am, 2005. 17(3): p. 269-77.

Reason for exclusion: Not a study; review paper on sleep apnoea and sedation.

Karan, S.B., et al., *Validation of a measurement to predict upper airway collapsibility during sedation for colonoscopy*. Journal of Clinical Monitoring and Computing, 2012. 26(6): p. 451-457.

Reason for exclusion: Wrong population: patients admitted for colonoscopy under sedation who are not using CPAP or denied OSA. Study on the effects of sedation on upper airway physiology for prediction of clinical interventions during sedation for colonoscopy.

Kaw, R., *Perioperative complications in patients with obstructive sleep apnea*. Sleep Medicine Clinics, 2013. 8(1): p. 129-134.

Reason for exclusion: Not a study; review paper.

Kaw, R., B. Gali, and N.A. Collop, *Perioperative care of patients with obstructive sleep apnea*. Current Treatment Options in Neurology, 2011. 13(5): p. 496-507.

Reason for exclusion: Not a study; opinion statement.

Khalid, O., et al., *Conscious sedation: For a TEE, is it always required?* Echocardiography, 2010. **27**(1): p. 74-76.

Reason for exclusion: Not a study; discussion paper on necessity of sedation for cardiac studies

Khiani, V.S, Salah, W., Maimone, S., Cummings, L., Chak, A. *Sedation during endoscopy for patients at risk of obstructive sleep apnea* GASTROINTESTINAL ENDOSCOPY Volume 70, No. 6 : 2009

Reason for exclusion: Wrong population; study on high risk for OSA patients.

Kim, G.H., et al., *Clinical predictors of apnoea-hypopnoea during propofol sedation in patients undergoing spinal anaesthesia**. Anaesthesia, 2012. **67**(7): p. 755-759.

Reason for exclusion: Wrong population; non-OSA patients received propofol infusion. This study assessed the occurrence of apnoea-hypopnoea during propofol sedation for spinal anaesthesia and predictive tests for OSA.

Kovoor, P., et al., *Efficacy and safety of a new protocol for continuous infusion of midazolam and fentanyl and its effects on patient distress during electrophysiological studies*. PACE - Pacing and Clinical Electrophysiology, 1997. **20**(11): p. 2765-2774.

Reason for exclusion: Wrong population; study on non-OSA patients.

Kreis, P., D.F. Kripke, and S. Ancoli Israel, *Sleep apnea: A prospective study*. Western Journal of Medicine, 1983. **139**(2): p. 171-173.

Reason for exclusion: Wrong study design; study on prevalence of OSA patients in medical ward.

Kumar, V., et al., *Low dose propofol and ketamine anesthesia for cardioversion allows obese patients to independently maintain a patent airway*. Anesthesia and Analgesia, 2011. **112**(5).

Reason for exclusion: Wrong population; study on non-OSA patients.

Lee, S.M., et al., *Does propofol and alfentanil-induced sedation cause periodic apnoea in chronic renal failure patients?* International Journal of Clinical Practice, 2010. **64**(1): p. 1-5.

Reason for exclusion: Wrong study design; study on chronic renal failure patients. Patients with chronic renal failure develop apnoea and hypopnoea more often than patients with normal renal function.

Li, S., et al., *Colonoscopy procedure related desaturation is associated with undiagnosed sleep apnea: A pilot study*. American Journal of Gastroenterology, 2011. **106**: p. S521-S522.

Reason for exclusion: Wrong study design. The purpose of this study is to see if moderate sedation for screening colonoscopy could be used as an assessment tool for sleep apnoea screening.

Liu SS, Chisholm MF, John RS, Ngeow J, Ma Y, Memtsoudis SG. *Risk of postoperative hypoxemia in ambulatory orthopedic surgery patients with diagnosis of obstructive sleep apnea: a retrospective observational study.* Patient Safety in Surgery 2010, 4:9.

Reason for exclusion: Wrong intervention.

Mador MJ *Do patients at risk of sleep apnea have an increased risk of cardio-respiratory complications during endoscopy procedures?* 2012. Sleep Breath 16(3):609–615

Reason for exclusion: Wrong population; study on high risk for OSA patients.

Mahowald, M.W. and M.A. Cramer Bornemann, *Sleep Disorders: Case Studies.* Neurologic Clinics, 2006. 24(2): p. 267-289.

Reason for exclusion: Case studies.

McArdle, P., *Intravenous analgesia.* Crit Care Clin, 1999. 15(1): p. 89-104.

Reason for exclusion: Not a study; discussion paper

McCall, W.V., et al., *What the electroconvulsive therapy practitioner needs to know about obstructive sleep apnea.* J ECT, 2009. 25(1): p. 50-3.

Reason for exclusion: Not a study; discussion paper.

Mealy, N.E. and M. Bayes, *SEP-174559/SEP-226332.* Drugs of the Future, 2004. 29(9): p. 971.

Reason for exclusion: No full paper found.

Mehta, P., et al., *Can a validated sleep apnea scoring system predict cardiopulmonary events during anesthesiologist-directed propofol sedation for routine egd and colonoscopy? A prospective cohort study.* American Journal of Gastroenterology, 2012. 107: p. S740-S741.

Reason for exclusion: Wrong population; study on patients with high risk or low risk for undiagnosed obstructive sleep apnoea.

Memtsoudis, S.G., et al., *Sleep apnea and total joint arthroplasty under various types of anesthesia: a population-based study of perioperative outcomes.* Reg Anesth Pain Med, 2013. 38(4): p. 274-81.

Reason for exclusion: Wrong intervention; analysis of peri-operative outcomes in patients undergoing total knee or hip arthroplasty under general, neuraxial, or combined neuraxial-general anaesthesia. No details provided by the authors in

regarding patients receiving intravenous sedation when neuraxial anaesthesia was administered.

Memtsoudis SG, Liu SS, Ma Y, Chiu Y-L, Walz JM, Gaber-Baylis LK, Mazumdar M. *Perioperative pulmonary outcomes in patients with sleep apnea after noncardiac surgery*. Anesthesia and Analgesia January 2011 Vol 112 Number 1.

Reason for exclusion: Wrong study design; analysis of a large national (United States) inpatient sample data for each year between 1998 and 2007. Peri-operative demographics and outcomes of patients with sleep apnoea after orthopaedic and general surgical abdominal procedures were studied.

Mendelson, W.B., *Safety of short-acting benzodiazepine hypnotics in patients with impaired respiration [1]*. American Journal of Psychiatry, 1991. **148**(10): p. 1401.

Reason for exclusion: Not a study; letter to the editor.

Meoli, A.L., et al., *Upper airway management of the adult patient with obstructive sleep apnea in the perioperative period--avoiding complications*. Sleep, 2003. **26**(8): p. 1060-5.

Reason for exclusion: Not a study; review paper on peri-operative risks and best management techniques for OSAHS patients (Report of the Clinical Practice Review Committee).

Mester, R., et al., *Monitored anesthesia care with a combination of ketamine and dexmedetomidine during cardiac catheterization*. American Journal of Therapeutics, 2008. **15**(1): p. 24-30.

Reason for exclusion: Wrong population; study on paediatric patients.

Miller, M.A., P. Levy, and M.M. Patel, *Procedural sedation and analgesia in the Emergency Department: What are the risks?* Emergency Medicine Clinics of North America, 2005. **23**(2): p. 551-572.

Reason for exclusion: Not a study; discussion paper on sedatives and analgesics.

Moos, D.D., *Obstructive sleep apnea and sedation in the endoscopy suite*. Gastroenterology nursing : the official journal of the Society of Gastroenterology Nurses and Associates, 2006. **29**(6): p. 456-463; quiz 464-465.

Reason for exclusion: Not a study; discussion paper.

Moos, D.D., et al., *Are patients with obstructive sleep apnea syndrome appropriate candidates for the ambulatory surgical center?* AANA Journal, 2005. **73**(3): p. 197-205.

Reason for exclusion: Not a study; discussion paper on safety of ambulatory patients receiving anaesthetic agents.

Neville, A., K. Coe, and J. Thompson, *How long is too long? Recovery time of outpatients with sleep apnea after procedural sedation*. *Gastroenterol Nurs*, 2013. **36**(4): p. 260-4.

Reason for exclusion: Not a study; discussion paper.

Ninger, L.J., *Safe care for patients with sleep apnea*. *OR Manager*, 2004. **20**(2): p. 25-7

Reason for exclusion: Not a study; discussion paper.

Ogan, O.U. and D.J. Plevak, *Anesthetic safety always an issue with obstructive sleep apnea*. *J Clin Monit Comput*, 1998. **14**(1): p. 69-70.

Reason for exclusion: Not a study; discussion paper.

Okwuone, C.O., et al., *Obstructive sleep apnea - Implications for procedural sedation*. *Journal of Radiology Nursing*, 2006. **25**(1): p. 2-6.

Reason for exclusion: Not a study. A discussion paper on pre-procedural evaluation, perioperative management and post-procedural care of the patients with sleep apnoea.

Olsen, J.W., R.L. Barger Jr, and S.K. Doshi, *Moderate sedation: What radiologists need to know*. *American Journal of Roentgenology*, 2013. **201**(5): p. 941-946.

Reason for exclusion: Not a study; discussion paper.

Parikh, S.N., et al., *Sleep apnea syndrome in patients undergoing total joint arthroplasty*. *Journal of Arthroplasty*, 2002. **17**(5): p. 635-642.

Reason for exclusion: Case report.

Passannante, A.N. and M. Tielborg, *Anesthetic Management of Patients with Obesity with and Without Sleep Apnea*. *Clinics in Chest Medicine*, 2009. **30**(3): p. 569-579.

Reason for exclusion: Not a study; discussion paper of the Practice Guidelines regarding the care of patients with obstructive sleep apnoea.

Poirier, P., et al., *Cardiovascular evaluation and management of severely obese patients undergoing surgery: A science advisory from the American Heart Association*. *Circulation*, 2009. **120**(1): p. 86-95.

Reason for exclusion: Not a study; recommendation paper for the pre-operative cardiovascular evaluation, intra-operative and peri-operative management and post-operative cardiovascular care of the OSA population.

Porhomayon, J., et al., *The management of surgical patients with obstructive sleep apnea*. *Lung*, 2011. **189**(5): p. 359-367.

Reason for exclusion: No primary data; review paper on management of surgical patients with OSA.

Ravveendran, R. Chung F., Perioperative Consideration of Obstructive Sleep Apnea in Ambulatory Surgery. *Anesthesiology Clin.* 2014. 32: p.321-328.

Reason for exclusion: No primary data; review paper on peri-operative precautions and post-operative management of patients with OSA.

Reid, J. and P. Picton, *CPAP facilitates sedation of patients with obstructive sleep apnoea [15]*. *Anaesthesia*, 2005. **60**(9): p. 941.

Reason for exclusion: No primary data; review paper.

Riley, R.W., et al., *Obstructive sleep apnea surgery: risk management and complications*. *Otolaryngol Head Neck Surg*, 1997. **117**(6): p. 648-52.

Reason for exclusion: Wrong study design; study on OSA patients undergoing maxillofacial procedures and surgery on airways.

Sabers C, Plevak D, Schroeder D, Warner D. *The diagnosis of obstructive sleep apnea as a risk factor for unanticipated admissions in outpatient surgery*. *Anesthesia and Analgesia* 2003;96:1328-35.

Reason for exclusion: Wrong study design. This study is comparing unplanned hospital admissions in OSA and non-OSA patients. Unplanned hospital admissions rates in patients with and without diagnosis of OSA scheduled for outpatient surgery were compared.

Spurr, K.F., et al., *Analysis of hospital discharge data to characterize obstructive sleep apnea and its management in adult patients hospitalized in Canada: 2006 to 2007*. *Canadian Respiratory Journal*, 2010. **17**: p. 5B-6B.

Reason for exclusion: Wrong study design; retrospective study on prevalence of sleep apnoea in acute care hospitals in Canada.

Society for Ambulatory Anesthesia consensus statement on preoperative selection of adult patients with obstructive sleep apnea scheduled for ambulatory surgery. - Joshi GP - *Anesth Analg* - 01-NOV-2012; 115(5): 1060-8 (MEDLINE® is the source for the citation and abstract of this record).

Reason for exclusion: Not a study.

Evidence-based patient safety advisory: patient assessment and prevention of pulmonary side effects in surgery. Part 1. Obstructive sleep apnea and obstructive lung disease. - Haeck PC - *Plast Reconstr Surg* - 01-OCT-2009; 124(4 Suppl): 45S-56S (MEDLINE® is the source for the citation and abstract of this record)

Reason for exclusion: Not a study.

Qadeer, M., et al., Hypoxemia during Moderate Sedation for Gastrointestinal Endoscopy: Causes and Associations. *Digestion*. 2011, **84**(37): p.37-45. (HAND SEARCHED ARTICLE)

Reason for exclusion: Wrong population; study on non-OSA patients. Study on relationship of sedation for GI endoscopy with endoscopic intubation and ventilation patterns.