



## EUROPEAN RESPIRATORY UPDATE

# Sedation for flexible bronchoscopy: current and emerging evidence

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**ABSTRACT:** Flexible bronchoscopy is commonly performed by respiratory physicians and is the gold standard for directly visualising the airways, allowing for numerous diagnostic and therapeutic interventions. With the widespread use of flexible bronchoscopy and the evolution of interventional bronchoscopy with more complex and longer procedures, physicians are placing increasing importance on the use of sedation as a necessary adjunct to topical anaesthesia. There is no standardised practice for the use of sedation in bronchoscopy with a good deal of variation among physicians regarding the use of pre-procedure medication and pharmacological sedatives. In addition, there is ongoing debate and controversy about proceduralist-administered *versus* anaesthetist-administered sedation whilst at the same time there is a growing body of evidence that nonanaesthetist administered sedation is safe and cost-effective. In this review we summarise the evidence for the use of sedation as an adjunct to topical anaesthesia in bronchoscopy and provide the clinician with up-to-date concise guidance for the use of pharmacological sedatives in bronchoscopy and future directions for sedation in the bronchoscopy suite.

**KEYWORDS:** Anaesthesia, bronchoscopy, midazolam, proceduralist administered, propofol, sedation

Flexible bronchoscopy is commonly performed by respiratory physicians and is the gold standard for directly visualising the airways, allowing for numerous diagnostic and therapeutic interventions. With the widespread use of flexible bronchoscopy and the evolution of interventional bronchoscopy with more complex and longer procedures, physicians are placing increasing importance on the use of sedation as a necessary adjunct to topical anaesthesia. Some physicians perform the procedure without sedation. Indeed, one study suggested that although midazolam may facilitate the performance of the procedure for the operator, it does not improve patient comfort [1]. Another study showed that with the proper patient selection, awake bronchoscopy is well tolerated [2]. However, the majority of physicians now use pharmacological sedatives [3] and anxiolytics, improving procedural tolerance and patient satisfaction, as shown by several case-control studies and randomised controlled trials [4–8]. There is no standardised practice for the use of sedation

in bronchoscopy with a good deal of variation among physicians regarding the use of pre-procedure medication and pharmacological sedatives [3, 9]. Only recently has more specific guidance been published on this by a society of respiratory specialists in the American College of Chest Physicians consensus statement [10]. In addition, there is ongoing debate and controversy about proceduralist-administered *versus* anaesthetist-administered sedation whilst at the same time there is a growing body of evidence that non-anaesthetist administered sedation is safe [11, 12] and cost-effective [13].

Topical anaesthesia is imperative for both patient and operator satisfaction but this topic is beyond the remit of this review. In this review we summarise the evidence for the use of sedation as an adjunct to topical anaesthesia in bronchoscopy (inpatient and outpatient setting) and provide the clinician with up-to-date concise guidance for the use of pharmacological sedatives in bronchoscopy and future directions for sedation in the bronchoscopy suite.

### MODERATE SEDATION

In most settings, sedation is not administered by an anaesthetist but by the bronchoscopist (proceduralist-administered sedation) who is ultimately responsible for the patient under their care. It is therefore important that the bronchoscopist can administer pharmacological sedatives safely to render depression of the level of consciousness to a level that is sufficient to carry out the procedure; achieving procedure tolerance without

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compromising the patient's ability to maintain a patent airway, and ventilatory and cardiovascular function. A moderate level of sedation should be achieved and this is sometimes referred to as conscious sedation whereby the techniques used are unlikely to render the patient unconscious and the patient is able to respond to verbal commands. If the patient is only responding to painful stimulus in the form of reflex withdrawal, then a level of deep sedation has been obtained and the ability to independently maintain ventilatory function or a patent airway may be impaired [14].

### SAFE DELIVERY OF MODERATE SEDATION

To achieve the required level of sedation, the chosen pharmacological sedative should be administered by titration of small incremental doses to the desired clinical and physiological effect, irrespective of being given in boluses or as a continuous infusion. This is particularly important in patients where the arm-brain circulation time (time taken for the drug to travel from the injection site to the brain and have its central nervous system effect) is prolonged (*e.g.* heart failure). In the elderly, dose adjustments are particularly important due to the reduced hepatic metabolism and renal function, reduced tissue and blood esterases and increased sensitivity to a given concentration of drug [15]. Dose adjustments may also be required in substance misusers, recipients of stem-cell transplants, patients with cystic fibrosis (after lung transplantation), American Society of Anesthesiology (ASA) physical status category 3 and 4 patients (especially those with severe renal or hepatic dysfunction), and where drug interactions enhancing or inhibiting their effects are used [16–18]. The depth of sedation should always be monitored throughout the procedure and documented using the Ramsay scale [19] (table 1). For moderate sedation a depth of sedation should not be greater than that of level 3. Bispectral (BIS) index monitoring is an electroencephalographic-based method of assessing a patient's level of consciousness and has been used in two trials of moderate sedation for bronchoscopy [20, 21]. Both studies concluded that BIS can be used safely by the non-anaesthetist to titrate sedation with propofol. Further studies are required to determine if the use of BIS monitoring is more cost-effective than the use of clinical judgement alone. Due to the risk of bradycardia, hypotension and respiratory depression associated with the use of pharmacological sedatives patients should be appropriately monitored with the continuous measurement of pulse rate and oxygen saturations, and frequent blood pressure.

Before commencing the procedure it may be useful that the bronchoscopist and the unit staff go through a checklist

**TABLE 1** Ramsay sedation scale

1	Patient is anxious and agitated or restless, or both
2	Patient is cooperative, oriented and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response

(table 2), adapted from the WHO surgical checklist [22], to ensure that they are adequately prepared to safely administer the sedation, perform the bronchoscopy and recover the patient. Each unit should have an adequately equipped post-procedure recovery with monitoring of respiratory and cardiovascular physiology and support to deal with potential complications. Monitoring should continue after completion of the procedure until complete recovery of sedation has been observed and recorded. Parameters that should be assessed as criteria for safe discharge should include stable vital signs, respiratory function with airway patency, adequate cardiovascular status and an awake, alert and comfortable patient. Time to reach these criteria can be highly variable based on patient factors and medication choices.

### PRE-MEDICATION DRUGS IN BRONCHOSCOPY

#### Anti-cholinergic drugs

Anti-cholinergic drugs, such as atropine and glycopyrrolate, have been used due to their sympathetic effects which can prevent vasovagal reactions (bradycardia), and reduce coughing and airway secretions which may improve procedure tolerance and visualisation of the airways. In the past they were used as standard practice by many bronchoscopists but in clinical trials these drugs have failed to demonstrate benefits in bronchoscopy. COWL *et al.* [23] and MALIK *et al.* [24] compared intramuscular atropine and glycopyrrolate to placebo. COWL *et al.* [23] found no significant benefit in the use of anti-cholinergics in reducing secretions, cough and complication rates or in increasing patient comfort. Despite demonstrating a reduction in airway secretions MALIK *et al.* [24] found no benefits on patient comfort, oxygen desaturation or the time it took to complete the procedure and there were greater haemodynamic fluctuations and rise in blood pressure and pulse rate with the use of atropine.

#### Clonidine

Clonidine, a centrally acting  $\alpha_2$ -adrenergic agonist, has been used due to the sympatholytic effects on the cardiovascular system that may reduce the incidence of arrhythmias and

**TABLE 2** Pre-sedation flexible bronchoscopy checklist

Patient identifier (name, date of birth)
Consent form signed
Responsible adult available to escort the patient post-procedure
Adequate fasting period
Allergies
Hepatic and renal function (if the clinical history suggests these could be abnormal)
Observations (vital signs)
Continuous pulse oximetry available
Intravenous access functioning
Medications checked
Resuscitation trolley available with emergency drugs
Reversal drugs available (flumazenil and naloxone)
Oxygen available (including variety of oxygen delivery devices)
All staff ready for the procedure to commence

Data from [22].

myocardial infarction during bronchoscopy, which is often associated with tachycardia and hypertension [25]. In a small randomised controlled trial, MATOT and KRAMER [26] showed that oral clonidine attenuated the haemodynamic response to flexible bronchoscopy but with higher doses ( $4\text{--}4.5\ \mu\text{g}\cdot\text{kg}^{-1}$ ) it resulted in hypotension. In a trial of intravenous clonidine, DE PADUA *et al.* [27] demonstrated the beneficial effect of clonidine on blood pressure and heart rate with a reduction in frequency in arrhythmias but didn't demonstrate an improvement in patient comfort. Clonidine is probably not used more frequently due the prolonged sedative effects of oral administration, the rebound hypertension seen occasionally on withdrawal of the drug and the lack of larger randomised controlled trials [28].

### **Labetalol**

Labetalol is an  $\alpha_1$ - and  $\beta_1/\beta_2$ -antagonist used for its ability to reduce peripheral vascular resistance and arterial blood pressure without causing a reflex tachycardia. FOX *et al.* [29] performed a randomised controlled trial of intravenous labetalol *versus* placebo in addition to midazolam–alfentanil sedation and found no beneficial effect of adding labetalol as patients appropriately sedated with midazolam–alfentanil had adequate attenuation of their sympathetic stress responses.

### **Dextromethorphan**

Dextromethorphan is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist with anti-tussive properties that has been used in bronchoscopy with midazolam sedation by SCHWARZ *et al.* [30]. Dextromethorphan (dose of 90 mg) led to a reduction in cough with less topical lignocaine and midazolam being required, whilst achieving better analgesia and patient comfort.

### **Fenoterol**

Fenoterol is an inhaled short-acting  $\beta_2$ -agonist. It was used pre-procedure in addition to intramuscular atropine and hydroxyzine by VESCO *et al.* [31] in a small, randomised controlled trial. Fenoterol, in addition to atropine was found to have significant anti-tussive effects leading to less topical lignocaine being used.

### **Codeine phosphate**

Codeine phosphate is an opiate with analgesic and anti-tussive properties and has been assessed by TSUNEZUKA *et al.* [32] in bronchoscopy as an adjunct to sedation with midazolam. The authors found that the addition of codeine phosphate  $0.4\ \text{mg}\cdot\text{kg}^{-1}$  given orally 60 min before the procedure led to a reduction in the dosage of topical anaesthetic and the degree of oxygen desaturation compared to placebo. Codeine is converted by cytochrome P450 2D6 (CYP2D6) to morphine but genetic polymorphisms exist that alter the conversion of the drug, leading to decreased effect in slow metabolisers and an increased effect and complications in ultra-rapid metabolisers [33]. The use of this drug has been replaced in bronchoscopy by newer short-acting opiates.

### **Benzodiazepines**

Lorazepam and temazepam have been found to improve patient comfort and willingness to undergo a future procedure and this was thought to be related to its amnesic effect as

patients were less likely to recall the procedure [34, 35]. These drugs have now been replaced by midazolam with more favourable properties and used in intra-procedural sedation.

With the present methods of sedation, pre-medication does not appear to be necessary to improve procedure tolerance and patient satisfaction. The administration of pre-medication may, in this case, lead to the potential of over-sedation and adverse effects. However, more trials of the use of clonidine and labetalol or other sympatholytic agents are needed to evaluate the effect on the reduction of arrhythmias and myocardial infarction.

## **PHARMACOLOGICAL SEDATIVES USED FOR SEDATION DURING BRONCHOSCOPY**

An ideal sedative for use in outpatient bronchoscopy should be easy to use, have a rapid onset, short duration of action, and rapid recovery with rapid return of cognition. It should have a predictable pharmacokinetic and pharmacodynamic profile that is not altered by interactions with other drugs and should be reversible with a predictable and specific antagonist. Ultimately, its properties and use should result in improved safety of the procedure, as well enhance patient comfort and tolerance. A summary of the properties of pharmacological sedatives commonly used in bronchoscopy are listed in table 3.

### **Benzodiazepines**

Benzodiazepines have a long history of safety and efficacy in bronchoscopy and are widely used for sedation. These drugs enhance the effect of the gamma-aminobutyric acid (GABA) and have sedative, hypnotic, anxiolytic, anti-convulsant and muscle relaxing properties [18]. In higher doses they may have amnesic-dissociative properties, which have been reported to be a reason why patients are less reluctant to have another bronchoscopy in the future if needed [34]. Another advantage is the ability to safely and effectively reverse their action with the antagonist, flumazenil, which must be available in every unit if these drugs are going to be used for sedation [37]. Benzodiazepines are metabolised in the liver *via* the cytochrome P450 (CYP) 3A4 and 3A5 system and excreted mainly in the urine. Due to natural variability in this system among various populations, the elimination half-life of these drugs may be prolonged in 5–8% of the population [38]. Midazolam has a large volume of distribution similar to diazepam but a short elimination half-life (2 h) and faster onset of action [18].

Benzodiazepines have relatively small cardiovascular depressant effects and only result in slight decreases in arterial blood pressure and increases in heart rate with some decrease in vagal tone resulting in heart rate variability seen with midazolam [18]. The ventilatory drive is depressed and although apnoea is not usually seen with low doses used for moderate sedation this may occur with higher doses, in those with comorbidities and when used in combination with other respiratory depressants.

Flumazenil, an imidazobenzodiazepine derivative, is a competitive antagonist of benzodiazepines at the GABA receptor and is used for reversal of benzodiazepine effects. It has a shorter half-life than the benzodiazepines used in bronchoscopy so its effect may cease before that of the benzodiazepine and lead to re-depression of the respiratory drive unless supplemental doses are given. It is essential that the patient is

**TABLE 3** Pharmacological properties of common sedatives used in bronchoscopy

Drug	Fentanyl	Alfentanil	Morphine	Midazolam	Lorazepam	Diazepam	Propofol 1%	Fospropofol
<b>Dose i.v.</b>	Initial: 25–50 µg Supplemental: 25 µg	Initial: 250 µg Supplemental: 250 µg	Initial: 2.5 mg Supplemental: 2.5 mg	Initial: 2–2.5 mg (0.5–1 mg in the elderly) Supplemental: 1 mg (0.5–1 mg in the elderly) at 2–5 min intervals	Initial dose: 1.5–2 mg Supplemental: usually not required Wait at least 10 min	Initial dose: 5–10 mg Supplemental: usually not required Wait at least 10 min	Initial: 10–50 mg titrated to effect Supplemental: 25% of initial dose Infusion: 25–100 µg·kg <sup>-1</sup> ·min <sup>-1</sup>	Initial: 6.5 mg·kg <sup>-1</sup> Supplemental: 1.6 mg·kg <sup>-1</sup>
<b>Onset of action</b>	3–5 min	Immediate	5–10 min	30–60 s	8–15 min	1 min	30–60 s	6.5 min
<b>Peak effect</b>	5 min	Immediate	15–30 min	5–10 min	15–30 min	2–3 min	2 min	12 min
<b>Duration of action</b>	1–2 h	1–2 h	1–6 h	30–120 min	8 h	1–3 h	4–8 min	17 min
<b>Metabolism</b>	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic
<b>Renal excretion</b>	<5%	<1%	90%	<1%	<1%	<1%	70%	70%
<b>Elimination half-life</b>	3–4 h	1–2 h	2 h	1.5–2.5 h	11–22 h	20–50 h	3–12 h	45 min
<b>Major/common adverse events</b>	Respiratory depression, nausea and vomiting	See fentanyl	See fentanyl	Respiratory depression, hypotension	See midazolam	See midazolam	Respiratory depression, bradycardia, hypotension, pain at the injection site	Respiratory depression, hypotension, paraesthesiae, pruritus
<b>Antagonists</b>	Naloxone 100–200 µg (1.5–3 µg·kg <sup>-1</sup> ) with supplemental doses of 100 µg every 2 min until reversal occurs	See fentanyl	See fentanyl	Flumazenil 0.2 mg, repeated every 60 s up to 1 mg; if a continuous infusion is required the dose is 0.1–0.4 mg·h <sup>-1</sup>	See midazolam	See midazolam	No antagonist available	
<b>Comments</b>	Combination with benzodiazepines may enhance respiratory depression Administer prior to the benzodiazepines, as a lower dose of benzodiazepine will be required to achieve the desired degree of sedation	See fentanyl	See fentanyl	Combination with opiates may enhance respiratory depression	See midazolam	See midazolam	Combination with opiates may enhance respiratory depression Dose and rate of administration should be adjusted according to desired level of sedation and response For patients >65 years or with severe systemic disease reduce the dose by 25%	See propofol

Adapted from [10, 18, 36].

appropriately monitored until the effect of the benzodiazepine has completely ceased without supplemental doses of the antagonist. For reversal of benzodiazepine sedation, the dose of flumazenil is 0.2 mg, repeated every 60 s up to 1 mg; if a continuous infusion is required the dose is 0.1–0.4 mg·h<sup>-1</sup> [39].

Lorazepam [34] and diazepam [4] have been used in bronchoscopy but midazolam is the most frequently used benzodiazepine due to its properties having advantageous effects over others, especially the rapid onset of action, rapid time to peak effect and short duration of action [18]. The doses used for sedation of midazolam, lorazepam and diazepam are 0.01–0.1 mg·kg<sup>-1</sup>, 0.03–0.05 mg·kg<sup>-1</sup> and 0.04–0.2 mg·kg<sup>-1</sup>, respectively [18]. In a recent randomised controlled trial, ROLO *et al.* [7] showed that patients sedated with midazolam had less cough and dyspnoea and had increased patient-reported comfort and willingness to have a repeat procedure compared with placebo. This has been previously shown by others, such as CASES VIEDMA *et al.* [40] who also showed that the use of midazolam, reduced operator difficulties in performing the procedure and procedure time. Midazolam has been used safely and effectively in combination with opiates [8].

### Opioids

Opioids are now frequently used in bronchoscopy in combination with benzodiazepines for their analgesic, anti-tussive and sedative properties. These properties complement those of the benzodiazepines, offering advantages in improving conditions for the bronchoscopist, improving patient tolerance of the procedure and attenuating sympathetic responses associated with intubation. At the same time it leads to a reduction in the amount of other pharmacological sedatives (*e.g.* benzodiazepines and propofol).

Opioids bind to mu ( $\mu$ ), kappa ( $\kappa$ ), delta ( $\delta$ ) and sigma ( $\sigma$ ) receptors that are found in the brain, spinal cord, peripheral sensory neurons and gastrointestinal tract [18]. The opioids used in bronchoscopy are agonists mainly of the  $\mu$  receptor, responsible for supraspinal analgesia, respiratory depression and muscle rigidity [18]. They are mainly metabolised by the liver and excreted in by the kidneys. Due to renal elimination, opioids (especially morphine) can accumulate (metabolites) in patients with renal failure leading to prolonged sedation and ventilatory depression. In high doses opioids lead to bradycardia and associated hypotension but do not depress cardiac contractility. The effects on the respiratory system are more noteworthy, particularly reduction of the respiratory rate resulting in ventilatory depression. Due to the effects of opioids on the respiratory centres in the brainstem the apnoeic threshold is increased and the hypoxic drive is reduced.

Naloxone is the competitive opioid antagonist at the  $\mu$ ,  $\kappa$  and  $\delta$  receptors. The intravenous dose for reversal of opioid respiratory depression and over sedation is usually 100–200  $\mu$ g (1.5–3  $\mu$ g·kg<sup>-1</sup>) with supplemental doses of 100  $\mu$ g every 2 min until reversal occurs to the desired level of respiration and consciousness [41]. With a short mean half-life of 64 min, over sedation may recur and an infusion or repeated dosing every 1–2 h [42] may be required.

Fentanyl is 100 times as potent as morphine and has a more rapid onset of action and elimination half-life making it more suitable for use in bronchoscopy [43]. The recommended dose

of fentanyl in moderate sedation is 50–200  $\mu$ g followed by supplemental doses of 50  $\mu$ g but, at the upper limit of this range, ventilatory depression is more likely, especially when co-administered with other sedatives; therefore, an initial dose of 25–50  $\mu$ g is recommended with supplemental doses of 25  $\mu$ g as required until the desired effect is achieved or a total dose of 200  $\mu$ g has been reached. Continuous infusion at a rate of 0.05–0.08  $\mu$ g·kg<sup>-1</sup>·min<sup>-1</sup> may also be used [42]. It is important to realise that in most circumstances doses of 200  $\mu$ g are not required and that the dose needs to be reduced when used in combinations with other sedatives. PAPAGIANNIS and SMITH [44] reported their observation of consecutive patients receiving either fentanyl (dose range 50–100  $\mu$ g) or midazolam (dose range 5–15 mg) in addition to pre-medication with oral lorazepam and atropine for flexible bronchoscopy. They did not report any significant differences between the two except for the reduction in cough in those receiving fentanyl.

Alfentanil is less potent than fentanyl, but it has an almost immediate onset of action and shorter elimination half-life [45]. An initial dose of 250–500  $\mu$ g is given followed by 250  $\mu$ g supplemental doses as required [45]. HOUGHTON *et al.* [46] conducted a randomised controlled trial of alfentanil *versus* midazolam for flexible bronchoscopy. They did not demonstrate large differences in outcomes between the two groups. Those receiving alfentanil had less cough but patients reported more discomfort. In the randomised controlled trial by HWANG *et al.* [47] the combination of propofol and alfentanil preserved haemodynamic stability throughout the procedure but mean oxygen saturation dropped below 90% (87.3±7.3%) after the initial bolus, immediately before the procedure, but this was transient with oxygen saturation levels returning to baseline after starting the procedure with no patients requiring assisted ventilation. When used in combination with midazolam, FOX *et al.* [29] found that these patients had adequate sedation and attenuation of sympathetic responses. DREHER *et al.* [48] compared consecutive patients with stable pre-existing respiratory failure undergoing flexible bronchoscopy receiving midazolam alone or midazolam-alfentanil combination. They did not find any differences in oxygen desaturation or hypoventilation but those in the combination group reported less discomfort. GREIG *et al.* [49] compared midazolam alone, alfentanil alone and midazolam-alfentanil combination for flexible bronchoscopy. Alfentanil provided adequate sedation and with its anti-tussive properties significantly attenuated coughing. The combination of midazolam-alfentanil though did not provide better sedation or improve patient tolerance and was associated with a greater risk of oxygen desaturation. The only advantage of alfentanil over fentanyl when used for moderate sedation is its quicker onset of action and shorter sedation time [50] although in bronchoscopy there have been no trials directly comparing these two short-acting opioids.

### Propofol

Propofol (2,6-diisopropylphenol) is a short-acting anaesthetic agent with a rapid onset of action that has been used in bronchoscopy for moderate sedation. It is rapidly metabolised, mainly by conjugation in the liver, with a short initial distribution half-life (2–8 min) and initial two-phase elimination half-life of 30–60 min allowing rapid recovery [18, 51]. It works by binding to the  $\beta$ -subunit of the GABA-A receptor

increasing the chloride conductance and results in hyperpolarisation of the post-synaptic membrane [18]. The major effects on organ systems are on the cardiovascular, respiratory and central nervous system and it is used for its hypnotic, anti-emetic and anti-pruritic effects but it does not have any analgesic properties. It causes a decrease in systemic vascular resistance and cardiac contractility resulting in a drop in the arterial blood pressure. Propofol can attenuate upper airway reflexes and can cause profound respiratory depression leading to apnoea at induction doses and in doses used for conscious sedation it can inhibit the hypoxic ventilatory drive. Propofol may cause pain on injection but this may be reduced by using the vein in the antecubital fossa, pre-treatment with opioids or pre-treatment with lignocaine together with venous occlusion if a hand vein is used [52].

Propofol is manufactured in a lipid-based oil emulsion that contains soybean oil, egg lecithin, and glycerol [51]. It is not necessarily contra-indicated in patients with egg allergy because most egg allergies are due to ovalbumin in the egg white and egg lecithin is extracted from highly purified egg yolk [53]. There is an increased risk of bacterial infection of propofol vials as it contains no anti-bacterial preservatives [51].

Propofol can be administered intravenously by bolus doses or as a continuous variable rate infusion but the latter is preferable to minimise undesirable cardiorespiratory effects. For induction of sedation a dose of 0.5–1 mg·kg<sup>-1</sup> over 1–5 min is usually required followed by maintenance concentrations of 1.5–4.5 mg·kg<sup>-1</sup>·h<sup>-1</sup> (concentrations needed for the maintenance of anaesthesia in normal individuals range 4–12 mg·kg<sup>-1</sup>·h<sup>-1</sup>) [51]. When administered as a sole agent, a single intravenous bolus dose of 0.5–1.0 mg·kg<sup>-1</sup> given at a rate of 40 mg over 10 s until the desired level of sedation is achieved (1–2.5 mg·kg<sup>-1</sup> for induction of anaesthesia) with top up doses of 25–50 mg every few minutes as required [51].

Randomised controlled studies of the use of propofol in bronchoscopy are summarised in table 4. These studies have demonstrated that sedation with propofol compared to no sedation leads to less cough, pain, sensation of asphyxiation, total amnesia and improved tolerance of the procedure with no differences in oxygen saturations between the groups [5]. Compared to sedation with midazolam, propofol has similar efficacy and safety [21] but faster onset of action and a more rapid patient recovery for propofol leading to early discharge [20, 21, 54–56] and improved patient tolerance [20, 21, 54–56]. Propofol can be administered with other pharmacological agents including opiates. This results in a lower required dose of propofol, improves sedation, reduces cough and provides analgesia [47, 58, 60, 61]. YOON *et al.* [57] compared propofol alone and the co-administration of propofol–alfentanil but did not find differences in patient or bronchoscopist satisfaction or in the degree of coughing, but those in the alfentanil group had significantly lower oxygen saturation levels. However, the lower levels of oxygen saturation reported in the alfentanil group are most likely not clinically significant. CARMÍ *et al.* [59] compared propofol to midazolam–alfentanil sedation whilst monitoring carbon dioxide tension and they found both to be equally safe but those in the midazolam–alfentanil group rather than the propofol group had higher carbon dioxide tension values and required more oxygen supplementation or airway support.

Due to the narrow therapeutic window between moderate sedation and anaesthesia with the use of propofol, and without the availability of an antagonist, it is generally recommended that it be used only by those formally trained in its use (*e.g.* anaesthetists) in an appropriate setting and with monitoring as used for deep sedation. Worldwide its use by non-anaesthetists remains controversial although in the literature it is extensively reported to have been used safely and effectively by non-anaesthetists either alone or in combination with other pharmacological sedatives [12, 56, 58, 62–67]. In the future, formal training and competency assessments in sedation practice for bronchoscopy may include the use of propofol given the evidence of benefit to patients.

### Ketamine

Ketamine has been used in flexible bronchoscopy and endoscopy, especially for the paediatric population [68, 69]. Ketamine is a structural analogue of phencyclidine, a non-competitive NMDA receptor antagonist and partial agonist at opioid  $\mu$ -receptors that has many central nervous system effects and dissociates the thalamus from the limbic cortex resulting in dissociative anaesthesia with the patient appearing conscious but unable to respond to sensory input [18]. It is biotransformed in the liver (mainly by CYP3A4) and excreted in the urine. It has a short-elimination half-life of 2 h [18]. In contrast to other pharmacological sedatives, ketamine results in an increased heart rate, cardiac output and arterial blood pressure due to stimulation of the sympathetic nervous system and inhibition of noradrenaline reuptake. When used alone it has minimal effect on ventilatory drive, generally preserving airway patency and respiratory function, but may cause apnoea when used in combination with other pharmacological sedatives and opioids. An advantage of ketamine is that it is a potent bronchodilator and analgesic, but it has the disadvantage of causing increased salivation and secretions, not attenuating upper airway reflexes and resulting in emergence delirium (*e.g.* confusion and hallucinations) in 10–20% of adults [70]. The latter may be reduced with the co-administration of midazolam or propofol [71, 72]. However, the co-administration of benzodiazepines with ketamine may result in a prolonged effect and attenuation of the cardiostimulatory effects of ketamine. Sympathetic antagonists such as  $\beta$ -blockers may unmask the myocardial depressant effects of ketamine. For moderate sedation, ketamine can be given intravenously as a bolus dose of 0.5 mg·kg<sup>-1</sup> and repeated every 5 min if required [36].

In the study of HWANG *et al.* [47], comparing the combination of propofol and alfentanil or propofol and ketamine *via* a patient controlled analgesia, ketamine was felt to be superior to alfentanil when combined with propofol. The sympathetic effects of ketamine maintained blood pressure values similar to pre-procedure levels and a higher percentage of patients in the propofol-ketamine group reported increased satisfaction with the procedure and demonstrated amnesia for the period of the bronchoscopy. The most commonly reported adverse effects by patients were delirium and hallucinations. As previously suggested [73], less propofol injection pain was seen in the propofol-ketamine group. A disadvantage to the use of ketamine is the longer duration of action compared to the other available sedatives currently used and the adverse effect of emergence delirium.

**TABLE 4** Summary of clinical studies of propofol in flexible bronchoscopy

Article	Study type	Drug	Main results
<b>CLARKSON [54]</b>	Randomised, double-blind, prospective-controlled study	Propofol (n=21) <i>versus</i> midazolam (n=20)	More rapid onset and recovery from sedation seen in the propofol group No significant difference in the amount of topical anaesthetic required or in oxygen desaturation
<b>CRAWFORD [55]</b>	Randomised, double-blind, prospective-controlled study	Propofol (n=21) <i>versus</i> midazolam–alfentanil (n=21)	In three patients in the midazolam–alfentanil and five in the propofol group the depth of sedation exceeded the moderate level Recovery to an appropriate level was more rapid in the latter group Oxygen saturations decreased in both groups and there were no significant differences in blood pressure Those in the midazolam group had more amnesia and longer recovery time
<b>GONZALEZ [5]</b>	Randomised, single-blind, prospective-controlled study	Propofol (n=9) <i>versus</i> no sedation (n=9)	Less cough, pain, sensation of asphyxiation, total amnesia and improved tolerance of the procedure in the propofol group No differences in oxygen saturations between the groups
<b>HWANG [47]</b>	Randomised, double-blind, prospective-controlled study	Propofol–alfentanil (n=138) <i>versus</i> propofol–ketamine (n=138) for patient-controlled sedation	Patients in the propofol–ketamine group reported greater amnesia and satisfaction Haemodynamic stability and adequate oxygenation during the procedure in both groups; however, a significant drop in oxygen saturations below 90% was seen in both groups immediately before the procedure This was transient and with no sequelae
<b>CLARK [20]</b>	Randomised, double-blind, prospective-controlled study	Propofol (n=43) <i>versus</i> midazolam (n=39)	Propofol resulted in faster recovery from sedation and patient tolerance and satisfaction were improved There were no differences in operator satisfaction Safely administered by non-anaesthetists
<b>STOLTZ [56]</b>	Randomised, non-blinded, prospective-controlled study	Propofol (n=100) <i>versus</i> midazolam–hydrocodone (n=100)	Mean oxygen saturation and desaturation below 90% were similar in both groups Patients receiving propofol had less tachycardia during the procedure and faster recovery from sedation
<b>GRENDLMEIER [12]</b>	Prospective case series	Propofol (n=440)	Systolic blood pressure dropped below 90 mmHg in 15.4% and oxygen saturation dropped below 90% in 16.4% of patients but some of these had higher American Society of Anesthesiology scores and were already hypotensive or hypoxaemic prior to the sedation None of the patients required intubation
<b>LO [21]</b>	Randomised, non-blinded, prospective-controlled study	Propofol (n=243) <i>versus</i> midazolam (n=249)	Bispectral index-guided propofol infusion is as safe as clinically judged midazolam sedation The proportion of patients with hypoxemia or hypotensive events were not different in the two groups but those in propofol group had the lowest mean arterial blood pressure and oxygen saturation readings Those in the propofol group had less cough, improved procedure tolerance and faster recovery from sedation
<b>YOON [57]</b>	Randomised, double-blind, prospective-controlled study	Propofol (n=32) <i>versus</i> propofol–alfentanil (n=32)	They did not find differences in patient or bronchoscopist satisfaction or in degree of coughing but those in the alfentanil group had significantly lower oxygen saturation levels. However, the lower levels of oxygen saturation reported in the alfentanil are most likely not clinically significant
<b>SCHLATTER [58]</b>	Randomised, double-blind, prospective-controlled study	Propofol (n=154) <i>versus</i> propofol–hydrocodone (n=146)	This combination suppressed coughing and reduced patient discomfort during flexible bronchoscopy compared to placebo alone with no differences in complication rates
<b>CARMÍ [59]</b>	Randomised, non-blinded, prospective-controlled study	Propofol (n=56) <i>versus</i> midazolam–alfentanil (n=59)	Those in the midazolam–alfentanil group rather than the propofol group had higher carbon dioxide tension values and required more oxygen supplementation or airway support; however, both were considered equally safe and effective

## EMERGING PHARMACOLOGICAL SEDATIVES IN BRONCHOSCOPY

### Fospropofol

Fospropofol, 2,6-diisopropylphenol methoxyphosphonic acid, is a water-soluble pro-drug of propofol and has a longer onset

and duration of action compared to the propofol lipid emulsion but has a much shorter elimination half-life [74]. Blood levels of propofol after administration of fospropofol reach lower peak levels and are more sustained than after administration of intravenous propofol leading to predictable

levels of moderate sedation [74]. The advantage of its use is that it does not cause pain on injection, does not have the high risk of bacterial contamination seen with propofol and leads to predictable levels of sedation, however, it has the disadvantage that if a patient is over sedated they will require ventilatory support for longer and is associated with the commonly reported adverse effects paraesthesiae and pruritus [75, 76].

COHEN and co-workers [76, 77] conducted two randomised controlled trials of fospropofol or midazolam following pre-medication with fentanyl for colonoscopy and found that a dose of 6.5 mg·kg<sup>-1</sup> provided appropriate sedation and high patient satisfaction. SILVESTRI *et al.* [6] conducted a phase III randomised controlled trial of fospropofol 2 mg·kg<sup>-1</sup> and 6.5 mg·kg<sup>-1</sup> (those >65 years of age or with ASA category 3 or 4 had the dose reduced by 25%). With the higher dose they found better sedation, absence of procedure recall and patient satisfaction. Hypoxia was seen in 15.4% of patients receiving the higher dose. In a subgroup analysis hypoxia was found to be more common in patients >65 years of age compared to younger patients (13.1% *versus* 9.0%, respectively) [78].

### Remifentanyl

Remifentanyl is  $\mu$ -opioid receptor agonist with an analgesic potency similar to that of fentanyl that undergoes rapid metabolism by non-specific esterases in blood and has a short half-life of <10 min [79]. The benefits of this being that its effects do not last long after discontinuing its administration irrespective of the duration of the infusion and there is no accumulation of the drug and metabolic toxicity in patients with hepatic dysfunction. In children sedated with propofol and remifentanyl full awakening was seen 5  $\pm$  1.3 min after stopping the remifentanyl infusion [80].

Remifentanyl has been used safely for flexible bronchoscopy in infants in combination with propofol [80, 81], but further studies are required to establish its role for flexible bronchoscopy compared with the other opiates. It is administered as an infusion at an initial rate of 0.1  $\mu$ g·kg<sup>-1</sup>·min<sup>-1</sup> and subsequently titrated in increments of 0.025  $\mu$ g·kg<sup>-1</sup>·min<sup>-1</sup> until the desired level of sedation is achieved but ideally shouldn't be >0.2  $\mu$ g·kg<sup>-1</sup>·min<sup>-1</sup> due to the increased risk of apnoea and chest wall rigidity [82].

### Dexmedetomidine

Dexmedetomidine is a selective  $\alpha_2$ -agonist with sedative and analgesic properties. It has the advantage of only causing mild respiratory depression at higher doses but does have sympathomimetic and vagolytic actions that may lead to bradycardia and hypotension [83]. These features are useful to attenuate the sympathetic response to intubation which it has been shown to do safely and effectively in flexible bronchoscopy for awake intubation [84] and in upper and lower gastrointestinal endoscopy [85–87], but it does require continuous cardiovascular monitoring to avoid unwanted complications. For upper gastrointestinal endoscopy dexmedetomidine resulted in a shorter recovery time and increased patient satisfaction when compared to midazolam [86]. Dexmedetomidine has been used successfully for bronchial thermoplasty [88] and recently for flexible bronchoscopy in a randomised controlled trial by RYU *et al.* [89]. Dexmedetomidine was co-administered with propofol and compared with propofol–remifentanyl combination. The

advantage of the dexmedetomidine was that it resulted in a lower incidence of oxygen desaturation and reduced need for oral cavity suction (reduced salivation and airway secretions), but it did result in prolonged recovery times, increased cough and lower bronchoscopist satisfaction scores when compared to remifentanyl. Dexmedetomidine does not have anti-tussive properties like the opioids so increased cough is expected and but further trials are required to determine the role of this drug in bronchoscopy.

### Remimazolam

Remimazolam is a novel short-acting GABA receptor agonist that is rapidly metabolised by non-specific tissue esterases and its action can be reversed with flumazenil [90]. Studies in sheep have shown that remimazolam has a more rapid onset of action and a shorter duration of action compared with midazolam but was associated with more pronounced respiratory depression and hypotension, similar to propofol [91]. In this study the respiratory depression correlated well with the depth of sedation. In a phase I trial in humans, it has been also been shown to have a faster onset of action and shorter duration of action than midazolam, without the resulting in the requirement for oxygen supplementation or ventilation with doses of 0.075–0.20 mg·kg<sup>-1</sup>.

### DRUG INTERACTIONS

Benzodiazepines, fentanyl, alfentanil and ketamine are metabolised by the CYP450 system (mainly CYP3A4). The action of CYP450 is altered by numerous drugs, which the bronchoscopist should be made aware of. Commonly used drugs such as the anti-retrovirals fluconazole, ketoconazole, erythromycin, diltiazem and cimetidine inhibit the CYP3A4 enzymes and prolong the effects of pharmacological sedatives [45]. This is of particular importance in patients on current antiretroviral treatment as these regimens contain either potent CYP3A4 inhibitors, such as the HIV protease inhibitor ritonavir, or enzyme inducers, such as the non-nucleoside reverse transcriptase inhibitors efavirenz or nevirapine [92]. Complications of the use of these drugs with antiretroviral treatment include prolonged sedation and arrhythmias and, in the study by HSU *et al.* [93], co-administration of protease inhibitors with intravenous midazolam was associated with severe prolonged sedation, as well as increased length of hospital stay.

### CONCLUSION

There is a definite need for anaesthetist delivered deep sedation (or general anaesthesia) for more prolonged and complex interventional pulmonology procedures. However, there should be further consideration of formal sedation training and credentialing for non-anaesthetists, supported by the currently available evidence that proceduralist-administered sedation is considered to be safe and cost-effective. Also, bronchoscopists need to be aware of the license available in their individual country for the use of the various pharmacological sedatives and practice within their competency. Higher-quality studies are needed to assess the efficacy of the emerging pharmacological sedatives as well as their cost-effectiveness in bronchoscopy, as the beneficial effects of individual sedatives on the process of clinical care, patient satisfaction and health resource utilisation may outweigh its acquisition cost.



Given the evidence, propofol is an important agent for moderate sedation with benefits for patients and should be an alternative to current sedation regimens in proceduralist-administered sedation provided the user is appropriately trained and local guidelines allow this use. In the meantime, midazolam in combination with a short-acting opioid (fentanyl or alfentanil) remain the pharmacological agents of choice for proceduralist-administered sedation in bronchoscopy. Timely discharge is a priority.

### STATEMENT OF INTEREST

None declared.

### REFERENCES

- Hatton MQ, Allen MB, Vathenen AS, *et al.* Does sedation help in fiberoptic bronchoscopy? *BMJ* 1994; 309: 1206–1207.
- Morris LG, Zeitler DM, Amin MR. Unsedated flexible fiberoptic bronchoscopy in the resident clinic: technique and patient satisfaction. *Laryngoscope* 2003; 117: 1159–1162.
- Smyth CM, Stead RJ. Survey of flexible fiberoptic bronchoscopy in the United Kingdom. *Eur Respir J* 2002; 19: 458–463.
- Putinati S, Ballerin L, Corbetta L, *et al.* Patient satisfaction with conscious sedation for bronchoscopy. *Chest* 1999; 115: 1437–1440.
- Gonzalez R, De-La-Rosa-Ramirez I, Maldonado-Hernandez A, *et al.* Should patients undergoing a bronchoscopy be sedated? *Acta Anaesthesiologica Scand* 2003; 47: 411–415.
- Silvestri GA, Vincent BD, Wahidi MM, *et al.* A Phase 3, randomized, double-blind study to assess the efficacy and safety of fospropofol disodium injection for moderate sedation in patients undergoing flexible bronchoscopy. *Chest* 2009; 135: 41–47.
- Rolo R, Mota PC, Coelho F, *et al.* Sedation with midazolam in flexible bronchoscopy - a prospective study. *Revi Port Pneumol* 2012; 18: 226–232.
- Ni YL, Lo YL, Lin TY, *et al.* Conscious sedation reduces patient discomfort and improves satisfaction in flexible bronchoscopy. *Chang Gung Med J*, 33: 443–452.
- Pickles J, Jeffrey M, Datta A, *et al.* Is preparation for bronchoscopy optimal? *Eur Respir J* 2003; 22: 203–206.
- Wahidi MM, Jain P, Jantz M, *et al.* American College of Chest Physicians consensus statement on the use of topical anesthesia, analgesia, and sedation during flexible bronchoscopy in adult patients. *Chest* 2011; 140: 1342–1350.
- Dang D, Robinson PC, Winnicki S, *et al.* The safety of flexible fiberoptic bronchoscopy and proceduralist-administered sedation: a tertiary referral centre experience. *Int Med J* 2012; 42: 300–305.
- Grendelmeier P, Kurer G, Pflimlin E, *et al.* Feasibility and safety of propofol sedation in flexible bronchoscopy. *Swiss Med Wkly* 2011; 141: w13248.
- Hassan C, Rex DK, Cooper GS, *et al.* Endoscopist-directed propofol administration *versus* anesthesiologist assistance for colorectal cancer screening: a cost-effectiveness analysis. *Endoscopy* 2012; 44: 456–464.
- American Society of Anesthesiologists. Continuum of depth of sedation: definition of general anesthesia and levels of sedation/analgesia. Park Ridge, ASA, 2009.
- Rivera R, Antognini JF. Perioperative drug therapy in elderly patients. *Anesthesiology* 2009; 110: 1176–1181.
- Chhajed PN, Wallner J, Stolz D, *et al.* Sedative drug requirements during flexible bronchoscopy. *Respiration* 2005; 72: 617–621.
- Chhajed PN, Aboyou C, Chhajed TP, *et al.* Sedative drug requirements during bronchoscopy are higher in cystic fibrosis after lung transplantation. *Transplantation* 2005; 80: 1081–1085.
- Morgan GE, Mikhail MS, Murray MJ, eds. *Clinical Anesthesiology*. 3rd Edn. New York, McGraw-Hill 2001.
- Ramsay MA, Savege TM, Simpson BRJ, *et al.* Controlled sedation with alphaxalone-alphadolone. *Br Med J* 1974; 2: 656–689.
- Clark G, Licker M, Younossian AB, *et al.* Titrated sedation with propofol or midazolam for flexible bronchoscopy: a randomised trial. *Eur Respir J* 2009; 34: 1277–1283.
- Lo YL, Lin TY, Fang YF, *et al.* Feasibility of bispectral index-guided propofol infusion for flexible bronchoscopy sedation: a randomized controlled trial. *PLoS One* 2011; 6: e27769.
- World Health Organization. Surgical Safety Checklist. First Edition. [www.who.int/patientsafety/safesurgery/tools\\_resources/SSSL\\_Checklist\\_finalJun08.pdf](http://www.who.int/patientsafety/safesurgery/tools_resources/SSSL_Checklist_finalJun08.pdf) Date last accessed: March, 21, 2013.
- Cowl CT, Prakash UB, Kruger BR. The role of anticholinergics in bronchoscopy. A randomized clinical trial. *Chest* 2000; 118: 188–192.
- Malik JA, Gupta D, Agarwal AN, *et al.* Anticholinergic premedication for flexible bronchoscopy: a randomized, double-blind, placebo-controlled study of atropine and glycopyrrolate. *Chest* 2009; 136: 347–354.
- Lundgren R, Häggmark S, Reiz S. Hemodynamic effects of flexible fiberoptic bronchoscopy performed under topical anesthesia. *Chest* 1982; 82: 295–299.
- Matot I, Kramer MR. Sedation in outpatient fiberoptic bronchoscopy: alfentanil-propofol *vs* meperidine-midazolam. *Anesthesiology* 1997; 87: A12.
- de Padua AI, de Castro M, Schmidt A, *et al.* Clonidine as a pre-anesthetic agent for flexible bronchoscopy. *Respir Med* 2004; 98: 746–751.
- Rupp H, Maisch B, Brilla CG. Drug withdrawal and rebound hypertension: differential action of the central antihypertensive drugs moxonidine and clonidine. *Cardiovasc Drugs Ther* 1996; 10: Suppl. 1, 251–262.
- Fox BD, Krylov Y, Leon P, *et al.* Benzodiazepine and opioid sedation attenuate the sympathetic response to fiberoptic bronchoscopy. Prophylactic labetalol gave no additional benefit. Results of a randomized double-blind placebo-controlled study. *Respir Med* 2008; 102: 978–983.
- Schwarz Y, Greif J, Lurie O, *et al.* Dextromethorphan premedication reduces midazolam requirement: objective and subjective parameters in peribronchoscopy. *Respiration* 2007; 74: 314–319.
- Vesco D, Kleisbauer JP, Orehek J. Attenuation of bronchofiberscopy-induced cough by an inhaled  $\beta_2$ -adrenergic agonist, fenoterol. *Am Rev Respir Dis* 1988; 138: 805–806.
- Tsunezuka Y, Sato H, Tsukioka T, *et al.* The role of codeine phosphate premedication in fibre-optic bronchoscopy under insufficient local anaesthesia and midazolam sedation. *Respir Med* 1999; 93: 413–415.
- US Food and Drug Administration. FDA Drug Safety Communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death. [www.fda.gov/Drugs/DrugSafety/ucm313631.htm](http://www.fda.gov/Drugs/DrugSafety/ucm313631.htm) Date last updated: August 16, 2012. Date last accessed: July 29, 2012.
- Maltais F, Laberge F, Laviolette M. A randomized, double-blind, placebo-controlled study of lorazepam as premedication for bronchoscopy. *Chest* 1996; 109: 1195–1198.
- Watts MR, Geraghty R, Moore A, *et al.* Premedication for bronchoscopy in older patients: a double-blind comparison of two regimens. *Respir Med* 2005; 99: 220–226.
- Fassoulaki A, Theodoraki K, Melemenis A. Pharmacology of sedation agents and reversal agents. *Digestion* 2010; 82: 80–83.
- Williamson BH, Nolan PJ, Tribe AE, *et al.* A placebo controlled study of flumazenil in bronchoscopic procedures. *Br J Clin Pharmacol* 1997; 43: 77–83.
- Dundee JW, Collier PS, Carlisle RJT, *et al.* Prolonged midazolam elimination half-life. *Br J Clin Pharmacol* 1986; 21: 425–429.
- eMC. Summary of Product Characteristics. Flumazenil 0.1 mg·mL<sup>-1</sup> solution for injection. [www.medicines.org.uk/EMC/medicine/](http://www.medicines.org.uk/EMC/medicine/)

- 26619/SPC/Flumazenil+0.1+mg+mL+solution+for+injection Date last updated: June 28, 2012. Date last accessed: July 28, 2012.
- 40 Cases Viedma E, Pérez Pallarés J, Martínez García MA, *et al.* [A randomised study of midazolam for sedation in flexible bronchoscopy]. *Arch Bronconeumol* 2010; 46: 302–309.
  - 41 eMC. Summary of Product Characteristics. Naloxone 400 micrograms/mL solution for Injection (hameln). [www.medicines.org.uk/EMC/medicine/21095/SPC/Naloxone+400+micrograms+mL+solution+for+Injection+\(hameln\)](http://www.medicines.org.uk/EMC/medicine/21095/SPC/Naloxone+400+micrograms+mL+solution+for+Injection+(hameln)) Date last updated: August 15, 2008. Date last accessed: July 30, 2012.
  - 42 Ngai SH, Berkowitz BA, Yang JC, *et al.* Pharmacokinetics of naloxone in rats and in man: basis for its potency and short duration of action. *Anesthesiology* 1976; 44: 398–401.
  - 43 eMC. Summary of Product Characteristics. Fentanyl 50 micrograms/mL Injection BP. [www.medicines.org.uk/EMC/medicine/27155/SPC/Fentanyl+50+microgram+mL+Injection/](http://www.medicines.org.uk/EMC/medicine/27155/SPC/Fentanyl+50+microgram+mL+Injection/) Date last accessed: March 25, 2013.
  - 44 Papagiannis A, Smith AP. Fentanyl *versus* midazolam as premedication for fibre optic bronchoscopy. *Respir Med* 1994; 88: 797–788.
  - 45 eMC. Summary of Product Characteristics. Alfentanil 500 micrograms/mL solution for injection. [www.medicines.org.uk/EMC/medicine/21358/SPC/Alfentanil+500+micrograms+mL+solution+for+injection](http://www.medicines.org.uk/EMC/medicine/21358/SPC/Alfentanil+500+micrograms+mL+solution+for+injection) Date last updated: July 27, 2011. Date last accessed: July 30, 2012.
  - 46 Houghton CM, Raghuram A, Sullivan PJ, *et al.* Pre-medication for bronchoscopy: a randomised double blind trial comparing alfentanil with midazolam. *Respir Med* 2004; 98: 1102–1107.
  - 47 Hwang J, Jeon Y, Park HP, *et al.* Comparison of alfentanil and ketamine in combination with propofol for patient-controlled sedation during fiberoptic bronchoscopy. *Acta Anaesthesiol Scand* 2005; 49: 1334–1338.
  - 48 Dreher M, Ekkernkamp E, Storre JH, *et al.* Sedation during flexible bronchoscopy in patients with pre-existing respiratory failure: midazolam *versus* midazolam plus alfentanil. *Respiration* 2010; 79: 307–314.
  - 49 Greig JH, Cooper SM, Kasimbazi HJ, *et al.* Sedation for fibre optic bronchoscopy. *Respir Med* 1995; 89: 53–56.
  - 50 Usta B, Türkyay C, Muslu B, *et al.* Patient-controlled analgesia and sedation with alfentanil *versus* fentanyl for colonoscopy: a randomized double blind study. *J Clin Gastroenterol* 2011; 45: e72–e75.
  - 51 eMC. Summary of Product Characteristics. Diprivan 1%. [www.medicines.org.uk/EMC/medicine/2275/SPC/Diprivan+1](http://www.medicines.org.uk/EMC/medicine/2275/SPC/Diprivan+1) Date last updated: January 26, 2012. Date last accessed: August 1, 2012.
  - 52 Jalota L, Kalira V, George E, *et al.* Prevention of pain on injection of propofol: systematic review and meta-analysis. *BMJ* 2011; 342: d1110.
  - 53 Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth Analg* 2003; 97: 1381–1395.
  - 54 Clarkson K, Power CK, Oconnell F, *et al.* A comparative evaluation of propofol and midazolam as sedative agents in fiberoptic bronchoscopy. *Chest* 1993; 104: 1029–1031.
  - 55 Crawford M, Pollock J, Anderson K, *et al.* Comparison of midazolam with propofol for sedation in outpatient bronchoscopy. *Br J Anaesth* 1993; 70: 419–422.
  - 56 Stolz D, Kurer G, Meyer A, *et al.* Propofol *versus* combined sedation in flexible bronchoscopy: a randomised non-inferiority trial. *Eur Respir J* 2009; 34: 1024–1030.
  - 57 Yoon HI, Kim JH, Lee JH, *et al.* Comparison of propofol and the combination of propofol and alfentanil during bronchoscopy: a randomized study. *Acta Anaesthesiol Scand* 2011; 55: 104–109.
  - 58 Schlatter L, Pflimlin E, Fehrke B, *et al.* Propofol *versus* propofol plus hydrocodone for flexible bronchoscopy: a randomised study. *Eur Respir J* 2011; 38: 529–537.
  - 59 Carmi U, Kramer MR, Zemtzov D, *et al.* Propofol safety in bronchoscopy: prospective randomized trial using transcutaneous carbon dioxide tension monitoring. *Respiration* 2011; 82: 515–521.
  - 60 Short TG, Plummer JL, Chui PT. Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. *Br J Anaesth* 1992; 69: 162–167.
  - 61 Mertens MJ, Olofsen E, Engbers FH, *et al.* Propofol reduces perioperative remifentanyl requirements in a synergistic manner: response surface modeling of perioperative remifentanyl-propofol interactions. *Anesthesiology* 2003; 99: 347–359.
  - 62 Jensen JT, Banning AM, Clementsen P, *et al.* Nurse administered propofol sedation for pulmonary endoscopies requires a specific protocol. *Dan Med J* 2012; 59: A4467.
  - 63 Cohen LB, Hightower CD, Wood DA, *et al.* Moderate level sedation during endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. *Gastrointest Endosc* 2004; 59: 795–803.
  - 64 Sipe BW, Scheidler M, Baluyut A, *et al.* A prospective safety study of a low-dose propofol sedation protocol for colonoscopy. *Clin Gastroenterol Hepatol* 2007; 5: 563–566.
  - 65 Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 2002; 96: 1004–1017.
  - 66 Bosslet GT, Devito ML, Lahm T, *et al.* Nurse-administered propofol sedation: feasibility and safety in bronchoscopy. *Respiration* 2010; 79: 315–321.
  - 67 Rex DK, Deenadayalu VP, Eid E, *et al.* Endoscopist-directed administration of propofol: a worldwide safety experience. *Gastroenterology* 2009; 137: 1229–1237.
  - 68 Berkenbosch JW, Graff GR, Stark JM. Safety and efficacy of ketamine sedation for infant flexible fiberoptic bronchoscopy. *Chest* 2004; 125: 1132–1137.
  - 69 Law AK, Ng DK, Chan KK. Use of intramuscular ketamine for endoscopy sedation in children. *Pediatr Int* 2003; 45: 180–185.
  - 70 Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med* 2008; 26: 985–1028.
  - 71 Sener S, Eken C, Schultz CH, *et al.* Ketamine with and without midazolam for emergency department sedation in adults: a randomized controlled trial. *Ann Emerg Med* 2011; 57: 109–114.e2.
  - 72 Andolfatto G, Willman E. A prospective case series of single-syringe ketamine-propofol (Ketofol) for emergency department procedural sedation and analgesia in adults. *Acad Emerg Med* 2011; 18: 237–245.
  - 73 Tan CH, Onsieng MK, Kua SW. The effect of ketamine pretreatment on propofol injection pain in 100 women. *Anaesthesia* 1998; 53: 302–305.
  - 74 Boules R, Szkiladz A, Nogid A. Fospropofol disodium (lusedra) injection for anesthesia-care sedation: a clinical review. *P.T.* 2012; 37: 395–422.
  - 75 Lusedra (fospropofol disodium) Injection, prescribing information. Woodcliff Lake, USA, Eisai Inc., 2009. [http://us.eisai.com/package\\_inserts/Lusedra%20PI.pdf](http://us.eisai.com/package_inserts/Lusedra%20PI.pdf) Date last accessed: August 1, 2012.
  - 76 Cohen LB, Cattau E, Goetsch A, *et al.* A randomized, double-blind, phase 3 study of fospropofol disodium for sedation during colonoscopy. *J Clin Gastroenterol*, 44: 345–353.
  - 77 Cohen LB. Clinical trial: a dose-response study of fospropofol disodium for moderate sedation during colonoscopy. *Aliment Pharmacol Ther* 2008; 27: 597–608.
  - 78 Silvestri G, Vincent B, Wahidi MM. Fospropofol disodium for sedation in elderly patients undergoing flexible bronchoscopy. *J Bronchol Interw Pulmonol* 2011; 18: 15–22.
  - 79 Bürkle H, Dunbar S, Van Aken H. Remifentanyl: a novel, short-acting,  $\mu$ -opioid. *Anesth Analg* 1996; 83: 646–651.
  - 80 Reyle-Hahn M, Niggemann B, Max M, *et al.* Remifentanyl and propofol for sedation in children and young adolescents undergoing diagnostic flexible bronchoscopy. *Paediatr Anaesth* 2000; 10: 59–63.
  - 81 Berkenbosch JW, Graff GR, Stark JM, *et al.* Use of a remifentanyl-propofol mixture for pediatric flexible fiberoptic bronchoscopy sedation. *Paediatr Anaesth* 2004; 14: 941–946.

- 82** eMC. Summary of Product Characteristics. Ultiva Injection. [www.medicines.org.uk/EMC/medicine/14766/SPC/Ultiva+Injection](http://www.medicines.org.uk/EMC/medicine/14766/SPC/Ultiva+Injection). Date last updated: January 4, 2011. Date last accessed: August 1, 2012.
- 83** Kamibayashi T, Maze M. Clinical uses of  $\alpha_2$ -adrenergic agonists. *Anesthesiology* 2000; 93: 1345–1349.
- 84** Bergese SD, Candiotti KA, Bokesch PM, *et al.* A phase IIIb, randomized, double-blind, placebo-controlled, multicenter study evaluating the safety and efficacy of dexmedetomidine for sedation during awake fiberoptic intubation. *Am J Ther*, 17: 586–595.
- 85** Demiraran Y, Korkut E, Tamer A, *et al.* The comparison of dexmedetomidine and midazolam used for sedation of patients during upper endoscopy: a prospective, randomized study. *Can J Gastroenterol* 2007; 21: 25–29.
- 86** Vázquez-Reta JA, Jiménez Ferrer MC, Colunga-Sánchez A, *et al.* [Midazolam *versus* dexmedetomidine for sedation for upper gastrointestinal endoscopy.]. *Rev Gastroenterol Mex*, 76: 13–18.
- 87** Dere K, Sucullu I, Budak ET, *et al.* A comparison of dexmedetomidine *versus* midazolam for sedation, pain and hemodynamic control, during colonoscopy under conscious sedation. *Eur J Anaesthesiol* 2010; 27: 648–652.
- 88** Lee JA, Rowen DW, Rose DD. Bronchial thermoplasty: a novel treatment for severe asthma requiring monitored anesthesia care. *AANA J* 2011; 79: 480–483.
- 89** Ryu JH, Lee SW, Lee JH, *et al.* Randomized double-blind study of remifentanyl and dexmedetomidine for flexible bronchoscopy. *Br J Anaesth* 2012; 108: 503–511.
- 90** Kilpatrick GJ, McIntyre MS, Cox RF, *et al.* CNS 7056: a novel ultra-short-acting Benzodiazepine. *Anesthesiology* 2007; 107: 60–66.
- 91** Upton RN, Martinez AM, Grant C. Comparison of the sedative properties of CNS 7056, midazolam, and propofol in sheep. *Br J Anaesth* 2009; 103: 848–857.
- 92** José RJ, Marshall N, Lipman MC. Important antiretroviral drug interactions with benzodiazepines used for sedation during bronchoscopy. *Chest* 2012; 141: 1125.
- 93** Hsu AJ, Carson KA, Yung R, *et al.* Severe prolonged sedation associated with coadministration of protease inhibitors and intravenous midazolam during bronchoscopy. *Pharmacotherapy* 2012; 32: 538–545.