Even though preterm labour may not be caused by the sedation process or the procedure itself, it remains a troublesome concern. The best strategy is to consult and involve the obstetrician well in advance of the procedure.

- Teratogenicity.

  Since the chances for teratogenicity during sedation are probably minimal to non-existent, pregnant patients can be reassured in this respect.

- Gastro-oesophageal sphincter tone are usually reduced and pregnant women often describe reflux symptoms. Depending on the type and duration of the procedure, general anaesthesia with airway protection should be considered.

10.3 Recovery

The patient must be allowed to recover from PSA in an appropriate and suitably equipped recovery room, with a healthcare professional trained in basic life support, monitoring him or her. The staff to patient ratio should not be less than one recovery professional to two patients. A medical practitioner should assume overall responsibility for patients in the recovery area and may not leave the premises until discharge criteria are met.

11. Drugs used in procedural sedation and analgesia

There is no ideal drug for PSA available yet, therefore combinations of drugs are often used. Most of the drugs used do not have both analgesic and sedative properties. The intravenous route is often used because of the predictable onset and offset of action.

Many of the maximum doses recommended here are lower than those quoted in the respective package inserts. This is because PSA frequently involves the administration of more than one type of drug. Drugs used for PSA can act in synergism when used in combination and it is suggested that the doses be reduced accordingly, and titrated in divided doses to effect. The sum of the incremental doses must not exceed the recommended maximum dose.

Where drug doses are not given in a weight-related dose (i.e. mg/kg), it must be assumed that it is the dose for a "standard" patient weighing 70 kg.

This guidance aims to promote good clinical practice through recommendations for the provision of sedation that is both safe and effective. It is not a recipe book for sedation techniques, nor how to do it. The guidance cannot replace training in specific sedation techniques that must include supervised clinical training.

This guidance is applicable to all patients receiving sedation to facilitate procedures, whether it is delivered in a surgery, in a community service clinic facility or in a hospital setting.

In general, the drugs selected for PSA should have a duration of action appropriate for the duration of the procedure. Sufficient time for peak brain effect (the target site) must be allowed, to prevent overdose of sedatives.

SASA recommends that general anaesthetic induction agents (propofol, ketamine, etomidate, dexmedetomidine) and the short-acting opioids (fentanyl, alfentanil, sufentanil, remifentanil) should only be used by those formally trained in anaesthesia or intensive care medicine, or by experienced sedation practitioners with anaesthetic experience who are trained in specific advanced sedation techniques. Sedation practitioners using these drugs must have *at least* a qualification in advanced life support.

Off-label and unlicensed drugs are sometimes used for adult PSA. Off-label drug use implies the use of licensed drugs outside the conditions of the license. Unlicensed drug use means the use of pharmaceutical products that have been approved by a licensing authority of a specific country. The unlicensed or off-label use of drugs is common practice worldwide, as well as in South Africa. Sedation practitioners are responsible for choosing the right drug and dose after careful consideration of expert opinion, scientific data on the drug(s), and what is published in the literature.

11.1 Sedatives

Sedatives do not produce analgesia and should not be used alone for painful procedures. Sedative drugs should never be used to compensate for inadequate analgesia.

Some patients may become disinhibited, restless and uncooperative with the use of sedatives. This scenario is important to recognise, as it may lead to stacking. Stacking occurs when restlessness is interpreted as patient anxiety, resulting in the administration of additional doses of the sedative. This may cause an unanticipated deepening of sedation to an undesirable level.

Caution must be exercised when combining benzodiazepines, or other sedatives, with opioids and other sedatives/analgesics. The effects of both categories of drugs are potentiated when used in combination, increasing the risk of respiratory compromise with possible airway obstruction, adverse events, and the progression to deeper levels of sedation. Titration remains a safe option in the administration of drugs.

Sedatives intended for procedural sedation include benzodiazepines (e.g. midazolam, diazepam, flunitrazepam, lorazepam, or temazepam) and dexmedetomidine. The most frequently used benzodiazepine is midazolam.

11.1.1 Benzodiazepines (BZDs)

The BZDs are the most commonly used sedative drugs in sedation practice and can be used by both operator-sedation practitioners for standard sedation techniques, and dedicated sedation practitioners as part of an advanced sedation technique.

11.1.1.1 Midazolam

Midazolam is a short-acting BZD with sedative, anxiolytic, amnestic, anticonvulsant and muscle relaxant effects. Since it has no analgesic effect, it should, when necessary, be combined with opioids during PSA.

It is the most commonly used benzodiazepine and has a clinical effect in 1–2 min, and a maximum effect after 13 min. Used in the recommended doses (Table 3), the administration of midazolam should result in a conscious, compliant patient.

Table 3: Dosing schedule of midazolam

Route of administration	Dose	Recommended maximum dose ***	Time to peak effect	Duration of action
Oral	0.25–0.5 mg/kg	7.5 mg	10–30 minutes	60 minutes*
Buccal/sublingual	0.25–0.3 mg/kg	7.5 mg	10–15 minutes	20–60 minutes*
Intravenous	0.05–0.1 mg/kg to a maximum bolus of 2 mg**	3 mg	3–5 minutes	20–60 minutes*
Rectal	0.5–0.75 mg/kg		10–20 minutes	60 minutes*
Intranasal	0.2–0.3 mg/kg	7.5 mg	10–15 minutes	20–60 minutes

* Dose-related
** Titrate to effect and repeat dose every 10 minutes until desired level of sedation is achieved, or recommended maximum dose is reached.
*** With elderly patients, it is advised that smaller intravenous doses must be titrated to effect.

The principal side-effect seen with intravenous administration of midazolam is that of respiratory compromise. Repeated doses should therefore be administered carefully to avoid complications such as airway obstruction and hypoxia. This is especially relevant in the elderly and patients with comorbidities. The drug should therefore be titrated to effect. The respiratory depression produced by midazolam has a synergistic relationship with the respiratory depression produced by other sedative drugs, especially the opiates. When used on its own in higher than recommended doses, midazolam administration is likely to result in the loss of upper airway muscle tone that may lead to airway obstruction. It produces minimal effects on the cardiovascular system in ASA I and II patients.

Paradoxical reactions, excitement and agitation occur in up to 15% of patients. Adding more midazolam may exacerbate the symptoms until severe respiratory depression and even unconsciousness are induced. In such cases, an alternative agent should be used to avoid this.

Ataxia and diplopia are other possible adverse effects associated with midazolam use. With severe side-effects like paradoxical reactions, the use of a BZD reversal agent, flumazenil, may be an option to administer to patients.

Nasal administration of drugs, like sedatives and analgesics, has become quite an exciting way of administering drugs. It can be considered in certain cases, e.g. needle phobias and special needs patients. The bioavailability of nasal midazolam is said to be about 80% which is superior to oral drugs.

Since intranasal midazolam can cause a burning sensation when administered, it is advised to use a mucosal atomisation device (MAD). Alternatively lignocaine 2% can either be administered before the intranasal midazolam or mixed with the solution to prevent burning of the nasal mucosae. Administration of midazolam may leave a bitter aftertaste that may last for several days. Careful selection of patients is necessary.

Intramuscular administration of midazolam is painful and not recommended.

The intravenous formulation can be given orally, mixed in a small volume of juice or paracetamol syrup to disguise the bitter taste. Once mixed, the shelf life is less than 24 hours. Tablets can be crushed and mixed in the same way to improve palatability.

11.1.1.2 Remimazolam

Remimazolam is a new benzodiazepine with a promising pharmacological profile, but still under evaluation in phase 3 trials.[15] It is metabolised by tissue esterases and has a rapid, more predictable offset of action than other clinically available benzodiazepines. Remimazolam has been developed for induction of anaesthesia and moderate or conscious sedation for minor invasive procedures. Remimazolam was found to be both faster acting and shorter lasting than midazolam, and showed a faster recovery time.

Remimazolam produces rapid dose-dependent sedation at doses from 0.075 mg/kg, with onset times of 1–3 min. It seems that remimazolam 0.075–0.20 mg/kg produces similar peak sedation to midazolam 0.075 mg/kg, but median recovery times at these doses ranged from 5 to 20 min, compared to 40 min for midazolam. This drug could be an exciting addition to the armamentarium of the sedation practitioner in future.

11.1.1.3 Buccolam

Buccolam is a new benzodiazepine that contains oro-mucosal midazolam in pre-filled oral syringes of 2.5 mg, 5 mg, 7.5 mg, and 10 mg. The solution, when administered, should be placed between the gums and cheek so that the drug is directly absorbed into the bloodstream.

11.1.1.4 Triazolam

Triazolam is a BZD which has been widely used for sedation/anxiolysis for intraoral procedures. The drug provides effective anxiolysis and amnesia. It is a useful sedative for PSA, as it has no active metabolites and is effective via the sublingual or oral routes (Table 4). Sublingual administration has been found to increase absorption by 28% over oral administration resulting in higher plasma concentrations at 1–2 hours. Sublingual triazolam (0.125–0.25 mg) achieves clinical effect within 20 minutes.

Table 4: Dosing schedule of triazolam

Route of administration	Dose	Recommended maximum dose	Time to peak effect	Duration of action
Oral/sublingual	0.125–0.5 mg	0.5 mg	90–120 minutes	6 hours

11.1.1.5 Temazepam

Temazepam is available exclusively for oral use. It has gained popularity in dentistry as an oral sedative for patients with learning difficulties. It has a half-life of 1.3–3 hrs, which means that it lasts longer than is ideal for an oral sedative for sedation. The drug is useful when administered by the operator-sedation practitioner in a dose of 20 mg two hours before the procedure.

Temazepam is also used for special needs patients, e.g. cerebral palsy, a dose 20 mg for hypnosis the evening before the procedure, and 20 mg an hour before procedural sedation.

Cimetidine, a H_2 receptor blocker, has been shown to increase blood levels of a metabolite of diazepam, and this has been implicated in delayed recovery. Temazepam is not affected by the H_2 receptor blockers; midazolam does not seem to be contraindicated in patients on H_2 receptor blockers.

If the patient becomes disinhibited and unmanageable after the administration of BZD, flumazenil, the specific BZD antagonist, should be considered to reverse the action of the BZD. Elective or urgent procedures should be abandoned and rescheduled, to be performed under general anaesthesia at a later date. In an emergency situation, immediate conversion to general anaesthesia may be considered, if appropriate.

11.1.2 Non-benzodiazepine sedatives

11.1.2.1 α_2-agonists

Two α_2-agonists, clonidine and dexmedetomidine, are used for sedation in clinical practice. They are sedative analgesics with anxiolytic, but not amnestic, effects. Used in recommended doses, they have minimal respiratory depressant effects. Oral agents are particularly useful in combination with simple analgesics for painful procedures.

Clonidine can be administered via multiple routes but, for the purposes of procedural sedation, the oral route is recommended (Table 5). It has a long duration of action as it is highly lipophilic.

In doses higher than those recommended for PSA, it can be used as an adjunct to lower the blood pressure and this may be requested by the surgeon for certain procedures. This practice should be carefully considered in the out-of-hospital environment. Clonidine may interact with various drugs, e.g. the antidepressants, and can cause rebound hypertension.

Table 5: Dosing schedule for clonidine

Dose	Onset of action	Time to peak effect
1–5 µg/kg	20–40 minutes	60 minutes

Dexmedetomidine is a highly selective α2-agonist (Table 6). It is a sedative, anxiolytic, hypnotic and sympatholytic, with analgesic properties. Dexmedetomidine is frequently referred to as the "ideal sedative", as it does not cause respiratory compromise and patients can be roused easily.

If needed for longer procedures, it needs to be administered by a slow initial bolus followed by a continuous infusion.[16] For adult patients, dexmedetomidine is generally initiated with a loading infusion of 1 (one) mcg/kg over 10 minutes. For patients over 65 years of age or those undergoing less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg over 10 minutes may be suitable. Maintenance dosing of dexmedetomidine should generally be initiated at 0.6 mcg/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hr for all procedures. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation. It is best to individualise dexmedetomidine dosing and titrate to the desired clinical effect.

Caution is required with the administration of dexmedetomidine as cardiovascular changes related to speed of injection can occur. Side-effects include profound bradycardia, sinus arrest and hypotension, particularly in patients with heart block or a high resting vagal tone. Cardiac arrest associated with the use of dexmedetomidine has been reported. Dexmedetomidine may also cause a dry mouth and nausea.

In South Africa, dexmedetomidine is licensed for use where sedation is administered in an operating theatre in a hospital setting and an intensive care setting.

Combinations of ketamine and dexmedetomidine are becoming increasingly popular for in-hospital use for PSA. Dexmedetomidine is increasingly being used for nasal and buccal administration for PSA in children.

Table 6: Dosing schedule of dexmedetomidine

Bolus dose	Maintenance infusion
0.5–1 µg/kg over 10 minutes	0.6 µg/kg/hour titrated to clinical effect (range = 0.2–1 µg/kg/hour)

11.1.2.2 Butyrophenones

Droperidol, a dopamine receptor antagonist, is a butyrophenone derivative with pharmacological and structural similarities to the neuroleptic haloperidol. Droperidol has sedative effects and is an excellent anti-emetic, but it lacks analgesic properties. Side-effects include hypotension, dysphoria and extrapyramidal movements. In high doses, droperidol prolongs the QT interval and may cause torsades de pointes and other malignant ventricular arrhythmias.

Droperidol is **not recommended** for use in PSA, because of the occurrence of dysphoria, prolonged sedation and the risk of hypotension, particularly when used in combination with other sedatives, or in the elderly. The recommended dose for the prevention and treatment of nausea and vomiting is 10 µg/kg; exceeding this dose prolongs recovery and increases the occurrence of side-effects.

11.2 Anaesthetic induction agents

11.2.1 Propofol

Propofol is a non-opioid, non-barbiturate, sedative/hypnotic drug and probably the most common and popular intravenous sedative agent. It has a rapid onset time of 30 to 60 sec and a short and predictable duration of action due to rapid equilibration between the blood and the brain. There is rapid redistribution of the drug to peripheral tissues and a rapid metabolic clearance from the blood. The half-life of propofol is 4.4 min. With the above characteristics, propofol is an ideal drug for PSA by trained sedation practitioners with airway certification.

Propofol can be used in small boluses titrated to effect. Due to its short context-sensitive half-time, it is a good drug to use as a continuous infusion, especially with the availability of TCI pumps (Table 7 and 8).

Propofol is a very effective hypnotic and amnestic. However, it has no analgesic properties. It is therefore usually combined with opioids during sedation for their synergistic effects. This may lead to significant cardiovascular depression and hypotension. Due to its narrow safety margin, deep sedation, airway obstruction and apnoea can occur rapidly and sometimes unpredictably. Patients must be carefully monitored.

Propofol should only be administered by an experienced sedation practitioner skilled in airway management and with anaesthetic experience. It is recommended that the drug not be used by an operator-sedation practitioner.

Propofol causes pain on injection in up to 90% of cases. The combination with lignocaine (0.1 ml of 2% lignocaine per 1 ml of propofol) or tramadol (20 mg) or ketamine 0.1 mg/kg injected intravenously before propofol administration, may reduce this.

Prolonged infusions of propofol have been associated with Propofol Infusion Syndrome (PRIS) and the development of fatal metabolic acidosis. The risk can be minimised by limiting propofol infusions to 80 µg/kg/minute (or 5 mg/kg/hour). In cases of prolonged sedation, patients must be carefully monitored for the development of PRIS.

For initiation of PSA, an infusion or slow bolus injection of propofol may be used. A rapid bolus injection can result in undesirable cardiorespiratory depression, including hypotension, airway obstruction, apnoea and desaturation. For maintenance of PSA, a variable rate infusion method is preferred to an intermittent bolus method.

Propofol is sterile, however it is a lipid-based emulsion, a vehicle known to support growth of micro-organisms. Sepsis and postoperative infection can occur as a result of unsafe practices, such as reuse of syringes on multiple patients, use of single-use medication vials for multiple patients, and failure to practise aseptic techniques.

Table 7: Dosing schedule for bolus doses of propofol

Dose	Titration	Onset of action	Repeat dose	Duration of action
Bolus 0.5mg/kg over 3–5 minutes*	1 minute	45–90 seconds	0.5 mg/kg	5–8 minutes

Table 8: Dosing schedule for infusion of propofol for PSA

Intravenous infusion	Target controlled infusion
2–4 mg/kg/hour titrated to clinical effect	Effect site concentration 1–2 µg/ml
In elderly patients, commence infusion at 1–2 mg/kg/hour	In elderly patients, recommended effect site concentration is 0.6–0.8 µg/ml

11.2.2 Ketamine

Ketamine is a phencyclidine derivative classified as an N-methyl-D-aspartate glutamate receptor antagonist (NMDA). Ketamine reduces the pre-synaptic release of glutamate, which is an excitatory neurotransmitter. The drug promotes central sympathetic stimulation and inhibition of neuronal catecholamine uptake.

Ketamine is available as a racemic mixture of two isomers, S (+) and R (-). This mixture is still used and very popular. Ketamine is, however, also available as a single isomer, S (+), Ketanest®.

Ketamine differs from other sedatives and has both analgesic and sedative characteristics. It can be used as the sole agent for painful procedures. It has a rapid onset of action (60–90 sec). Ketamine dissociates the thalamo-neocortical and limbic systems (emotional brain). The CNS is in effect dissociated from outside stimuli, i.e. pain, sight, sound (unpleasant experiences). The dissociative state caused by ketamine is characterised by sedation, intense analgesia, amnesia, intact protective reflexes, and stable cardiovascular parameters. These characteristics make ketamine such an attractive/safe and popular drug when used for procedural sedation.

The increasing popularity of ambulatory surgery has created a tremendous interest in ketamine for PSA. This is because of its short duration of action when used as boluses and in low doses, safety profile (used in small doses by the trained sedation practitioner), possibility of administration via many routes, the postoperative analgesic effects, and compatibility with other drugs. The drug has become a key component of advanced sedation techniques for medical and dental procedures. It must, however, be noted that the drug is not advised for use by single operator-sedation practitioners.

The multiple actions and cardiovascular stability of ketamine make it a very useful agent for painful procedures. Ketamine inhibits the catecholamine uptake, which exerts a sympathomimetic effect. It can increase the heart rate and blood pressure when higher doses are used. These side-effects are rarely seen with the doses recommended for PSA. Recent studies show that ketamine does not increase intracranial pressure at doses used for PSA.

Ketamine does not cause respiratory depression when titrated and injected slowly. Rapid intravenous administration may lead to intense respiratory depression. The laryngeal reflexes are usually intact with the doses used for PSA. What makes the drug extremely useful is its bronchodilatory properties. It is believed that ketamine protects against hypoventilation during deeper levels of sedation.

Ketamine stimulates the production of saliva and trachea-bronchial secretions. These effects are minimal with the low doses of ketamine recommended for PSA. There is no consensus on the use of prophylactic co-administration of anti-sialogogues and the concomitant use of a prophylactic anti-sialogogue is seldom necessary in adult patients. However, atropine may be a better drug than glycopyrrolate when administered with ketamine. Studies show a higher incidence of adverse events, e.g. nausea and vomiting, postoperative agitation, and airway obstruction when ketamine is used with glycopyrrolate.

Emergence of delirium may be associated with the use of ketamine in adults. Midazolam can be co-administered (≤ 0.05 mg/kg) to reduce the incidence of delirium.

Other reported reactions, such as ataxia, nystagmus, myoclonus, random limb movements and opisthotonus are rarely clinically important with the doses of ketamine recommended for PSA. Nausea and vomiting may occur, but are dose-dependent effects, and are more significant with intramuscular administration.

Ketamine can be given via multiple routes (Table 9), including intranasally. A burning sensation in the nose is possible, so lignocaine can be used before ketamine administration.

The versatility, efficacy, safety profile, and low cost of ketamine have promoted its widespread use and inclusion in the WHO list of "Essential Medicines" for a basic healthcare system.

Sedation practitioners must note that ketamine has become a very popular recreational drug.

Table 9: Dosing schedule of ketamine

Route of administration	Dose	Onset of action	Time to peak effect	Duration of action*
Oral	4–6 mg/kg as single agent, 2 mg/kg if used with other sedatives or analgesics	> 5 minutes	30 minutes**	4–6 hours
Intravenous	0.5–1 mg/kg***	1.5 minute	3–5 minutes	5–10 minutes
Intramuscular	2–4 mg/kg	2–5 minutes	20 minutes	30 minutes**
Rectal	4–6 mg/kg	> 5 minutes	30 minutes**	30–120 minutes**
Nasal	5 mg/kg	10 minutes	20 minutes	1 hour

* Duration of action is prolonged if ketamine is administered with other sedatives/analgesics.
** Dose-related
*** Titrate to effect and repeat dose every 10 minutes if necessary, until desired level of sedation achieved.

11.2.3 Etomidate

Etomidate is an intravenous drug that offers an alternative to provide procedural sedation, with maintenance of cardiovascular and respiratory function. Etomidate produces sedation and anxiolysis and is a useful alternative intravenous agent for procedural sedation in patients who may be allergic to propofol, e.g. egg allergy. It has no analgesic properties, therefore the addition of analgesics for painful procedures is recommended.

The side-effects of etomidate include myoclonus, nausea and vomiting and transient adrenal suppression. These side-effects are seldom seen at the doses administered for PSA (Table 10).

Table 10: Dosing schedule of etomidate

Route of administration	Bolus dose	Continuous infusion	Onset of action	Duration of action
Intravenous	0.1 mg/kg titrated to effect, then 0.05 mg/kg every 3–5 minutes as needed	0.2–0.3 mg/kg/hour*	1 minute	10–15 minutes, full recovery within 30 minutes

* About 0.1 ml/kg/hour titrated to effect.

11.3 Analgesics

11.3.1 Opioids

Opioids are analgesic drugs capable of inducing varying degrees of analgesia and sedation. Many different opioids are now available to relieve pain during procedures. Synthetic opioids such as alfentanil, fentanyl, sufentanil and remifentanil are extremely useful to supplement sedatives for short painful, and longer, procedures.

Respiratory and cardiac depression, particularly when used in combination with other respiratory depressant drugs (e.g. midazolam), may occur if not titrated to effect for PSA. Although opioids may have sedative side-effects, they **must not primarily** be used to sedate patients for either painless or painful procedures.

Opioids potentiate the effects of other sedatives, and cause dose-related depression of respiration and the central nervous system. When a sedative/opioid combination is used, the drug doses should be reduced and titrated to effect. The sedation practitioner must be trained and competent in the practice of rescue and resuscitation, should the need arise.

When given rapidly, opioids can induce chest wall and glottic rigidity. Opioids slow down gastrointestinal motility and can induce nausea and vomiting.

Capnography is highly recommended when potent opioids are administered, and meticulous clinical monitoring of respiratory and cardiovascular parameters throughout the procedure and recovery period is imperative. Whenever opioids are used for PSA, the specific antagonist naloxone must be immediately available.

11.3.1.1 Fentanyl and alfentanil

Fentanyl and alfentanil are potent short-acting opioids and probably the most popular drugs for use in PSA outside of the operating theatre (Tables 11 and 12). They have a safe and rapid onset and offset of effect, which are usually predictable and precise. They are easily titrateable and have reduced or rapidly reversible side-effects. Although short-acting opioids may be safely used in various applications, potential side-effects such as bradycardia, hypotension, respiratory depression, postoperative nausea and vomiting, and shivering are possible.

Short-acting opioids have significant potential for respiratory and cardiac depression, particularly in combination with other respiratory depressant drugs e.g. midazolam. Practitioners administering these drugs intravenously should be experienced sedation practitioners with airway management skills.

The doses of fentanyl and alfentanil, when used in combination with other depressant drugs (such as midazolam), should be decreased and titrated to effect. There is no specific dose, only a maximum dose. Slow titration of small boluses will decrease, but not eliminate, the possibility of adverse events. Monitoring of respiratory depressant effect remains crucial.

These drugs should not be used in patients at risk of upper airway obstruction since administration of fentanyl or alfentanil may precipitate this event and should be avoided. The short-acting opioids must also be used carefully in the elderly, the obese, and patients with obstructive sleep apnoea. Alternative analgesics are recommended.

Extreme care should be exercised in the post-procedural period, when the stimulus of the procedure has passed, but the drug is still active and more likely to cause respiratory depression.

Table 11: Dosing schedule of fentanyl

Route of administration	Dose	Onset of action	Time to peak effect	Maximum dose	Duration of action
Oral/transmucosal	5–15 µg/kg	15–30 minutes	30–45 minutes		1 hour*
Intravenous	0.25 µg/kg**	3– 6 minutes	2–3 minutes	2 µg/kg	30 minutes*

* Dose-related
** Titrate to effect and repeat dose every five minutes, until desired level of analgesia is achieved.

Alfentanil is an extremely popular short-acting opiate and can be used in small titrated boluses or as an infusion. If a continuous infusion is maintained for > 30 minutes, the context-sensitive half-time is longer than that of fentanyl. In this situation, the monitoring period after the infusion has been discontinued must be lengthened accordingly. The drug has a rapid onset and short duration of action, making it useful for short, painful procedures. Sedation practitioners must take cognisance of this short duration of action when the drug is administered prior to the painful stimulus. If the procedure is expected to take longer than 10 minutes, then either titrated bolus doses or an infusion technique can be used.

Table 12: Dosing schedule of alfentanil

Bolus dose	Titration interval	Time to peak effect	Duration of action of bolus	Infusion rates
In divided doses, up to a maximum of 5 µg/kg*	1.5 minutes	90–150 seconds	< 5 minutes	10–12 µg/kg/hour 0.25–1 µg/kg/minute

* When administered as a bolus, the drug must be titrated according to effect.

11.3.1.2 Sufentanil

Sufentanil is an extremely potent opioid analgesic (Table 13). When used in balanced general anaesthesia, it is 5–10 times as potent as fentanyl. There are few reports of its use in PSA in the literature, as it is mainly reserved for use in the intensive care setting in intubated and ventilated patients, or in patients undergoing general anaesthesia. Sufentanil is twice as lipophilic as fentanyl and is rapidly absorbed from the nasal mucosa. It is a useful analgesic when administered via this route.

Table 13: Dosing schedule of sufentanil

Route of administration	Dose	Time to peak effect	Duration of action
Intranasal	1 µg/kg	20 minutes	> 60 minutes
Intravenous bolus	0.02 µg/kg	5.6 minutes	30 minutes
Intravenous infusion	0.2–0.4 µg/kg/hour	6.5 minutes	240 minutes after a 2-hour infusion

11.3.1.3 Remifentanil

Remifentanil is an extremely potent, ultrashort-acting opiate that can be used in combination with hypnotic sedatives to provide sedation and analgesia. The drug is cleared by nonspecific blood and tissue esterases (whereas other short-acting opiates require hepatic clearance). Remifentanil should not be used outside the hospital environment, and must not be administered by any personnel other than anaesthetists or highly trained sedation practitioners with anaesthetic experience. For PSA, small bolus doses can be titrated, but with extreme care. The dose administered by continuous infusion must not exceed 0.05 µg/kg/minute.

Remifentanil when used with propofol for PSA should be administered in a separate syringe. Precise titration of remifentanil when used in combination with propofol should be achieved by using TCI.

Short-acting opiates commonly used for PSA outside the hospital environment:

The short-acting opioids have pharmacokinetic/pharmacodynamic profiles that are characterised by rapid onset and offset, enabling faster induction and emergence rates, making them excellent analgesic agents for PSA.

Onset and offset rates of short-acting opioids:

Pharmacokinetics	Remifentanil	Sufentanil	Alfentanil	Fentanyl
Onset	1.6 min	6.2 min	0.96 min	6.6 min
Offset: context-sensitive half-time	–6 min	30 min*	50–55 min*	> 100 min

* Context-sensitive half-time is the time required for a drug concentration in blood or at effect site to decrease by 50%; the above times are based on a 3-hour infusion. Of note is that alfentanil has a prolonged duration of action when used as a continuous infusion.

Opioids act in synergy with hypnotics and sedatives to produce a clinical effect and must be used carefully. Titration is recommended.

11.3.2 Tramadol

Tramadol is an atypical opioid (Table 14). It is an agonist at the µ-opioid receptor, but also inhibits re-uptake of noradrenaline and serotonin. Its use with serotonergic agents is contraindicated due to an increased risk of serotonin syndrome. Tramadol can be used in combination with propofol for PSA for painful procedures, as it rarely causes respiratory depression. Tramadol should be used with caution in patients taking psychotropic medication, and not be administered with 5HT3 receptor antagonists (e.g. granisetron, ondansetron).

Table 14: Dosing schedule of tramadol

Route of administration	Dose	Maximum dose	Time to peak effect
Oral	50–100 mg	400 mg/day	40 minutes
Intravenous	1–2 mg/kg over 5 minutes	400 mg/day	20 minutes, with duration of action up to 9 hours

11.3.3 Nitrous oxide (N_2O_2)

N_2O_2 is an anaesthetic agent with analgesic and sedative properties. It has a rapid onset and offset of action, and an excellent safety profile. Nitrous oxide is available in pure form or as Entonox®, premixed in a 1:1 (50% of each) ratio with oxygen.

The success of nitrous oxide sedation depends on appropriate titration of nitrous oxide to the individual patient's response and should be supported by behaviour management techniques.

Nitrous oxide sedation is very popular for use by operator-sedation practitioners for PSA and is usually used for brief, simple procedures. It is recommended that a second individual should monitor the patient and assist the operator-sedation practitioner. The recommended dose is between 20–50% (Table 15) and, in most cases, it will need to be supplemented, for example, with local anaesthesia. If other sedatives are administered, respiratory depression must be anticipated. Used in a concentration of < 50%, nitrous oxide produces minimal sedation and analgesia and at this concentration only clinical monitoring is necessary.

When used in a concentration of > 50%, nitrous oxide produces moderate sedation and analgesia or conscious sedation. The patient must then be monitored with a pulse oximeter and a blood pressure apparatus in addition to clinical monitoring. With concentrations above 50%, supplemental oxygen should be continued for several minutes after N_2O_2 has been discontinued in order to counter the possibility of diffusion hypoxia. N_2O_2 diffuses into air-filled cavities and should not be used in patients with chest injuries where pneumothorax is possible, in head injuries where pneumocranium is possible, or in patients in whom bowel obstruction is suspected.

When nitrous oxide is used as a sole agent for sedation, fasting is not necessary and pulse oximetry is not routinely required.

Dedicated, purpose-designed machines for the administration of inhalation sedation should be used. Such machines must conform to current standards and be maintained according to manufacturers' guidance with regular, documented servicing. Dedicated inhalation sedation machines will not allow hypoxic levels of sedation.

Gas cylinders must be stored safely and be secured with regard to current regulations to prevent injury.

Scavenging of waste gases must be active and sufficient to fully conform to current safety standards.

Table 15: Dosing schedule of nitrous oxide

Dose	Onset of action	Time to peak effect
50% in oxygen	30–60 seconds	3–120 minutes

11.3.4 Methoxyflurane

Methoxyflurane is a highly potent inhalational anaesthetic agent. It was mostly abandoned from general anaesthesia for renal toxicity. It has however been reintroduced in clinical practice for use in procedural sedation as a self-administered analgesic. A simple hand-held inhalator device filled with a fixed 3 ml vial of methoxyflurane for 20–30 min is used. Even though the use of methoxyflurane is controversial, it is claimed that the occupational hazards and organ toxicity are negligible with the low dose used.[17]

11.3.5 Local/regional anaesthesia

A significant number of procedures for PSA are done under local/regional anaesthesia. The sedation practitioner must be aware of which local anaesthetic agent is used, the possible adverse events, and the dose administered by the surgeon. The effective use of local anaesthetic agents plays a significant part in the success of PSA. Local anaesthetic agents can be used topically, for infiltration, or for local or regional nerve blocks.

Local anaesthetics are cardiac depressants. Toxicity may occur if used in amounts exceeding the recommended dose.

Warming and alkalinising the local anaesthetic solution can reduce the sting on infiltration.

EMLA® (Eutectic mixture of local anaesthetics of lidocaine 2.5% and prilocaine 2.5%) is available as a cream or a patch for topical anaesthesia usually before cannulation in extremely anxious patients. It requires up to two hours to achieve full effect and can be used on intact or broken skin. The patch is probably the best option for topical anaesthesia. EMLA® has a penetration depth of 3–12 mm.

EMLA® should not be used in patients allergic to any ingredient in EMLA® cream, e.g. patients allergic to the ester local anaesthetic agents or suffering from methaemoglobinaemia.

11.3.6 Simple analgesics

Simple analgesics are analgesics that, in the recommended doses, do not cause sedation. They are extremely useful agents for use by sedation practitioners as part of a PSA technique. They can be used pre-, intra-, and postoperatively.

Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used, but the time to onset of action must be taken into consideration before a procedure is performed (Table 16.

It is sometimes indicated to use a weak opioid, e.g. tramadol, for patients that still have significant pain after taking paracetamol and the NSAIDs.

Table 16: Dosing schedule of simple analgesics

Drug	Route of administration	Dose	Time to peak effect
Paracetamol	Oral	15–20 mg/kg	15–120 minutes
	Rectal	40 mg/kg	60–240 minutes
	Intravenous	15–20 mg/kg	30 minutes
Ibuprofen	Oral	7–10 mg/kg (400–800 mg every 4 hours)	120–240 minutes
Diclofenac	Oral	1–1.5 mg/kg	30–120 minutes
Ketorolac	Intravenous	0.5–1 mg/kg (10 mg every 8 hours)	60–120 minutes
	Intranasal	0.5 mg/kg (10 mg every 8 hours)	
Parecoxib	Intravenous	40 mg	Effective within 20 minutes, duration up to 9 hours

11.4 Antagonists

11.4.1 Flumazenil

Flumazenil (Table 17) reverses the sedative and respiratory depressant effects of BZDs. It should be readily available whenever BZDs are used. Its duration of action is approximately one hour, and resedation may occur if large doses of BZD have been administered. In such cases, the patient should be carefully monitored for at least two hours with a view to repeating the flumazenil dose. In an emergency, if intravenous access is not available, the intravenous dose can be given intranasally.

In patients taking BZD for seizures or behavioural disturbances, administration of flumazenil may precipitate these symptoms.

Table 17: Dosing schedule of flumazenil

Dose	Titration interval	Recommended maximum dose	Duration of action
10 µg/kg over 30 seconds*	2 minutes*	1 mg/kg	1 hour

* Repeat dose until desired effect achieved, or recommended maximum dose is reached.

It is not appropriate to administer flumazenil with the purpose of expediting the discharge of the patient from the sedation unit. Flumazenil should be reserved for use in inadvertent

overdose, unanticipated deepening of sedation, or respiratory compromise. Its use may be considered if severe paradoxical reactions occur with benzodiazepines.

11.4.2 Naloxone

Naloxone is a specific opioid antagonist (Table 18). It will reverse the respiratory depressant effects and analgesic effects of opioids, and should be readily available whenever opioids are administered. Naloxone should only be used for severe respiratory depression or respiratory arrest, as reversal of analgesia may cause a profound sympathetic response. Since its duration of action is short, respiratory depression may recur, requiring additional doses. Monitoring should continue for at least two hours after the administration of naloxone. Once there has been a good clinical response to an intravenous dose of naloxone, additional administration of the total effective dose may be given as an intramuscular injection, thereby providing a depot of the drug and minimising the risk of a recurrence of respiratory depression. In an emergency, if intravenous access is not available, the initial doses may be given intramuscularly. It can also be administered intranasally.

NB. These are the recommended doses for use in postoperative opioid respiratory depression, not the doses recommended for the treatment of opioid overdose.

Table 18: Dosing schedule of naloxone

Route of administration	Dose	Titration interval*	Maximum dose**	Duration of action
Intravenous	0.08–0.2 mg	2 minutes	10 mg	45 minutes

* Repeat dose until desired effect achieved or maximum dose reached.
** Postoperative respiratory depression should be reversed after administration of doses far lower than the maximum permissible dose.

If postoperative respiratory depression fails to respond to a dose of 0.4 mg, an alternative diagnosis should be sought.

11.5 Novel therapies

11.5.1 Ketofol

Ketofol is a combination of ketamine and propofol, that can be administered together in the same syringe, or independently in two separate syringes, with the one following the other. The literature suggests that the combination can be safely mixed in the same syringe. There has been increasing interest in the mixture for PSA and the combination has become extremely popular.

Ketofol can be used as bolus for PSA for short procedures, or boluses combined with an intravenous infusion for longer procedures using TCI.

The combination of ketamine and propofol (ketofol) probably enables the use of lower doses of both drugs, thereby minimising adverse events like respiratory depression. Propofol mixed with racemic ketamine is popular for PSA. The optimal combination (ratio) and optimal infusion rate are the focus of research studies. It will probably depend on the level of sedation that is planned. It is advised to use as low as possible a dose of ketamine in the mixture. The addition of ketamine to propofol infusion will prolong recovery unless infusion rates are decreased.

Addition of ketamine to propofol infusion resulted in delayed recovery when a ratio of 1:1 was used.[18]

It is suggested that a 10:1 propofol-ketamine mixture provides the greatest benefit for continuous intravenous sedation in adults undergoing surgery. Better haemodynamic stability and faster recovery times will be achieved with this mixture. Lowering the ketamine concentration may also be associated with earlier discharge times.[19]

11.5.2 Melatonin

Melatonin is a neurohormone produced by the pineal gland. It is synthesised from tryptophan via 5-hydroxytryptamine (serotonin). Melatonin is produced commercially by chemical synthesis, or from the pineal glands of cattle.

Melatonin induces natural sleep, with no known complications or risk of respiratory compromise. It has been used in the treatment of primary and secondary sleep disorders, the prevention and treatment of jet lag, and successfully used as a sedative for premedication. Melatonin provides anxiolysis and sedation. Unlike midazolam, it has minimal effects on cognitive and psychomotor skills after recovery.

Melatonin is administered as a sublingual preparation. Doses of 0.05 mg/kg of melatonin have been used to provide preoperative anxiolysis and sedation. The drug is most effective when administered during the period in which the patient would normally be asleep.

11.5.3 Trazodone

Trazodone is a triazolopyridine. It is mostly used for the treatment of depression, but also has sedative effects. Trazodone can be used as an alternative if paradoxical reactions to midazolam have previously been recorded. An extended-release tablet is also available which should be used on an empty stomach at bedtime.

Usual adult dose

Immediate-release tablets: Initial dose: 150 mg per day in divided doses.
Extended-release tablets: Recommended starting dose: 150 mg once daily.

11.5.4 Zaleplon

Zaleplon is a short-acting sedative/hypnotic with an ultrashort half-life. It is chemically unrelated to the benzodiazepines, although it has similar effects due to its affinity for the same receptors on nerve cells. The drug has less residual central nervous system ("hangover") effects than the benzodiazepines. Zaleplon causes less anxiolysis but more profound hypnosis than the benzodiazepines, although it does not interfere with sleep architecture.

The pharmacokinetics of zaleplon makes it an ideal drug for PSA. It has an average onset of activity of 15 to 20 minutes after oral administration, an approximate duration of action of four hours, and is extensively metabolised in the liver. There are no active metabolites. Side-effects include drowsiness and headache.

Zaleplon has been effectively used as a hypnotic for patients undergoing dental extractions, with 5–20 mg of oral zaleplon producing comparable anxiolysis to triazolam. Recovery from zaleplon is faster than recovery from triazolam.