Sedation in the Emergency Department: A Complex and Multifactorial Challenge

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*The Wand is only as good as the Wizard**

Introduction

Why Procedural Sedation and Analgesia?

Painful therapeutic procedures are frequently necessary during emergency care of children, many of whom already have a painful and frightening injury or illness. Immobility for diagnostic radiological procedures in young children is also often required. These procedures are distressful for the children, their parents, and their healthcare providers. Inadequately relieved procedure-related pain and distress produces physiological and psychological reactions that have acute and long-term consequences [1–6].

Safe and effective management of procedure-related pain and anxiety in the emergency department (ED) has become expected [7]. It facilitates controlled accomplishment of therapeutic and diagnostic procedures [3, 8, 9], reduces psychological trauma and its sequelae [3, 5, 8, 10], reduces healthcare provider and parental distress, and improves parental acceptance of rendered care [11]. Many advances in procedural sedation and analgesia (PSA) for nonelective procedures in non-fasted patients in the ED have occurred over the past 20 years as a result of intense interest in this concept and the development of general and pediatric emergency medicine specialties, for whom PSA is now considered core training [12]. Family and third-party payer's desire for definitive management of acute injuries during initial ED visits also seems to be increasing. This chapter reviews some of the PSA techniques shown to safely and effectively decrease children's pain and anxiety associated with procedures in the ED. Since pain and anxiety are frequently indistinguishable, the combination will often be referred to as distress.

Long-Term Negative Impact of Painful Procedures

Elimination or relief of pain and suffering, whenever possible, is an important responsibility of physicians caring for children [13], as unmanaged pain can result in a variety of negative long-term consequences [14]. Accumulating evidence indicates that by the middle of the third trimester of human gestation, ascending pain fibers fully connect to the primary somatosensory cortex of the brain [15, 16]. Descending inhibitory pain pathways, on the other hand, appear to require postnatal development. Rather than being less sensitive to pain, young infants may actually experience pain more intensely than older children [17]. As the brain rapidly matures during the first weeks to months after birth, recurrent painful

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stimuli may alter the formation of new neuronal circuits, resulting in children's hypersensitivity and increased behavioral response to noxious stimuli [15, 18–23].

Inadequately controlled procedure-related pain has been correlated to increased distress and maladaptive behaviors during subsequent healthcare interactions. Boys circumcised at birth without effective anesthesia had increased distress at their 4- and 6-month routine vaccinations compared to uncircumcised controls [24]. Similarly, toddlers who had painful postoperative care during the first 3 months of life demonstrated greater pain responses at their 14-month immunizations compared with controls [25]. In older children, painful therapeutic procedures have been associated with negative memory and greater pain during similar future procedures [26–28], even when those future procedures are performed with adequate analgesia [5]. Although the mechanisms underlying these observations have yet to be fully elucidated, these studies show that painful episodes can be encoded into children's implicit and explicit memories [23]. While praising a child following a painful procedure, in an effort to modify negative memories, may lessen these memories and reduce distress during subsequent procedures [29], prevention of negative memories by employing effective sedation-analgesia for intensely painful procedures is likely a crucial part of preventing the negative feedback loop that can then cause greater anxiety and pain during future procedures and healthcare interactions [30, 31].

When May PSA Not Be Needed?

PSA requires substantial and frequently scarce healthcare resources in a busy ED and has significant, albeit rare, risks. Emergency healthcare providers therefore increasingly are employing strategies that provide effective minimally painful techniques for local anesthesia or systemic analgesia. Combined with psychological or behavioral approaches to reduce patient anxiety, these strategies may greatly reduce the need for PSA as well as diminish the need for deeper sedation [32].

Nearly Painless Local Anesthesia

Topical Anesthetics

Use of topical anesthesia for children's lacerations has become standard in many EDs. Locally compounded solutions or gels containing 4% lidocaine, 0.1% epinephrine (adrenaline), and 0.5% tetracaine (LET or LAT), provide local anesthesia when instilled for 20–30 min into an open wound or abscess [33–35]. These solutions are more effective in scalp and facial lacerations than those on extremities or the trunk but their initial use markedly reduces the pain of subsequent injection of lidocaine, if such is needed. Careful application of limited amounts of these solutions onto lip or mucous membrane lacerations, e.g., using a cotton-tip swab, has been shown safe and can be quite effective [36]. Caution must be used, especially in small children, as rapid absorption of the anesthetics could cause toxicity. A recent study also found use of LET on finger lacerations safe and effective [37].

Buffering Injected Lidocaine

Pain associated with injection of lidocaine can be markedly reduced by buffering the anesthetic, injecting slowly through fine needles (e.g., 30-gauge) subcutaneously instead of intradermally, and warming the anesthetic to body temperature [38–42]. Buffering lidocaine, with or without epinephrine, to pH 7.0–7.2 by mixing 1 part of 1 mEq/mL sodium bicarbonate with 9–10 parts of 1% lidocaine markedly decreases the pain of injection [43, 44]. Buffering also decreases onset time for anesthesia [44] without affecting efficacy or duration [44–46]. The buffered mixture is stable for at least 3 weeks when stored at room temperature [45] and longer when refrigerated [47].

Psychological Interventions Reduce Distress and Need For PSA

Acute injury or illness causes significant anxiety and stress for most children and their parents. Lack of understanding of ED routines for care,

ongoing pain, prolonged waits, preconceived notions about emergency care, and numerous other known and unknown factors interfere with effective preparation of the child and use of the child's and parents' coping mechanisms [48]. Consequently, many young children are frightened and unwilling to cooperate with necessary procedures, even when little or no pain is involved. A warm smile and a slow respectful and sometimes playful approach may reduce the frightened child's perception of the provider as a threat and increase the likelihood of cooperation without need for sedation. Addressing parental concerns and providing them with an explanation of the plan for care, along with age-specific suggestions on how they can allay some of their child's fears and anxieties, allows them to prepare their child as well as themselves.

Having their parent at their side during painful procedures in the ED is of utmost importance for school-aged and younger children, despite realizing their parent can do little to alleviate procedural pain [49]. Parents likewise believe their presence during procedures is important and beneficial to their children [50–52]. EDs increasingly are enacting policies to give parents the option of staying with their child during all procedures and resuscitations, usually with a staff member dedicated to explain the care provided and to monitor the parent for signs of extreme distress, syncope, etc [53–55]. When suggestions are given to parents on how to help their child, e.g., touching, distracting with stories, reciting the alphabet, counting, etc, parents can provide significant assistance in accomplishing anxiety provoking procedures without sedation [56, 57]. In addition, nonthreatening language should be used to characterize anticipated sensations, e.g., "freezing, poking, or squeezing" instead of "burning, bee sting, or hurting." Simply allowing young children to sit in their willing parent's lap, with parents providing distraction and hugs for mild restraint, markedly reduces the child's distress during minor procedures [58]. Combining this technique with L.E.T. for topical wound anesthesia, supplemented as needed with buffered lidocaine injected via a 30 gauge needle, the author rarely finds it necessary to employ PSA for suturing lacerations in young children.

What Makes ED PSA Different?

Children often exhibit significant distress when faced with ED procedures despite administration of analgesic medications and psychological interventions. They may be anxious about sounds and sights they do not understand, fearful because of prior experience or hearsay, or in pain because of incomplete analgesia or local anesthesia. Furthermore, their usual coping mechanisms may be in disarray because of the unexpected nature of their illness or injury and their perception that they have no control over the impending treatment. When children refuse or are unable to cooperate with necessary procedures or if effective local anesthesia is not possible, safe and effective pharmacologic sedation can avert detrimental patient, parent, and practitioner sequelae and facilitate accomplishment of the procedure [5, 59, 60].

ED PSA in children, however, has greater inherent risks when contrasted to elective sedation. Patients frequently have not fasted for traditional periods and consequently may have "full stomachs" [61–63]. Postponement of procedures to allow fasting in the ED may be impractical due to limited resources. More importantly, postponement to allow gastric emptying is likely ineffective because painful injuries and serious illnesses unpredictably delay emptying of stomach contents; moreover, necessary administration of opioids for pain management likely exacerbates this problem. Compounding these issues, children undergoing painful or anxiety provoking procedures typically require deeper levels of sedation than adults or teenagers who may be able to better control their behavior [1]. Unanticipated arrival or deterioration of other ED patients and overextended ED staff may result in the sedating physician unpredictably being pulled away or distracted by other patients' emergencies. Finally, therapeutic procedures performed by trainees in academic EDs frequently are more prolonged and require longer periods of sedation.

Deciding Whether to Perform PSA

The first and foremost goal of pediatric PSA is assurance of the patient's safety and welfare during the sedation and recovery. With this in mind and the limitations noted earlier, the clinician considering PSA must carefully consider the following:

1. *Is the procedure necessary?* Some procedures that would require PSA in many children may be unnecessary. For example, it is likely that, as in adults, many lacerations of the hand and feet heal as well with bandaging as with suturing [64]. Similarly, virtually all tongue lacerations heal well without suturing [65].
2. *Do I have the resources and skills to rescue if rare but serious adverse events occur?* For example, would I be able to administer a paralytic drug for severe laryngospasm or secure the airway by intubation?
3. *What if an unexpected patient with a critical emergency arrives?* Do I have the resources to continue the PSA and procedure? Or, if I had to leave the patient, do I have the resources to safely recover the patient?

Systematic Approach to Safe ED PSA

Goals of PSA

Pediatric PSA by experienced providers has inevitable risks of adverse events including respiratory depression, apnea, airway obstruction, vomiting, hypotension, and dysphoria [66]. The first and foremost goal of pediatric PSA is assurance of the patient's safety and welfare during the sedation and recovery [59, 67]. Within this context, additional goals include control of behavior (muscle relaxation or relative immobility) and minimization of procedure-related pain, anxiety, memory, and negative psychological responses [59]. Safe attainment of these goals requires careful patient screening for factors associated with increased sedation-related risk of adverse events or difficult airway management, preparation for management of possible adverse events, and meticulous assurance of effective patient cardiopulmonary and other vital functions during and after the procedural sedation.

By developing a routine or systematic approach for ED PSA, the emergency physician reduces risks for the patient by identifying children at increased risk of adverse events and increasing preparedness for safe and effective management of adverse events, should they occur [68]. The systematic approach should include the following steps:

1. Pre-sedation patient assessment
2. Informed consent
3. Plan for sedation
4. Documentation/sedation record
5. Recovery/discharge
6. Quality improvement

1. *Pre-sedation patient evaluation and risk assessment*: Children should be screened for factors that may be associated with increased risk of adverse events or difficult management of these events during sedation. Identification of these risks allows for better preparation for management of untoward events or development of alternative plans to reduce the likelihood of undesired effects. In addition to general sedation screening in preparation for an ED procedure, a focused physical exam immediately prior to sedation should be repeated to detect any acute changes in the child's physiological status such as acute onset of wheezing or fever.

   Pre-sedation *history and physical examination* should focus upon the patient's cardiorespiratory status and airway to determine the sedator's ability to rescue breathe for this individual, if necessary [59, 69, 70]. A focused history may be guided by the mnemonic *AMPLE*:

   (*A*) Allergies to medications, latex, CT contrast, food (e.g., egg allergy prohibits use of propofol, shellfish allergies are associated with CT contrast reactions)

   (*M*) Current Medications or illicit drugs that might interact with PSA medications; these often reveal concurrent diagnoses that may impact PSA choices, e.g., psychiatric medications

(*P*) Past medical history, including any complications with sedation or anesthesia and chronic illnesses; history of snoring/stridor, recent URI/respiratory infections or asthma exacerbations, GERD, cardiac history, prematurity, any neuromuscular disease (may contraindicate succinylcholine), and history of airway surgery/tumors/malformations

(*L*) Last meal/fluid intake

(*E*) Events leading to need for procedure, e.g., associated injuries

(a) ASA physical status classification

The patient physical status classification endorsed by the American Society of Anesthesiologists (ASA) [71] to predict risk for adverse events during general anesthesia [72, 73] is helpful in assessing sedation risks and is summarized in Table 15.1. ASA Class I and II children are at low risk for serious adverse events when carefully monitored. Events which are initially minor, such as upper airway obstruction during deep sedation, usually can be easily addressed with simple interventions and catastrophic sequelae prevented. However, children with underlying illnesses often have less cardiopulmonary reserve and thus a greater risk for adverse responses to sedative and analgesic medications and their rescues often are more difficult and complex. Therefore, when possible, it is suggested an experienced sedation provider or anesthesiologist be consulted for planning sedation of ASA Class III patients and an anesthesiologist consulted for Class IV or V patients.

(b) Airway assessment: comorbid risk factors, Mallampati classification

Factors associated with difficulty in airway management include those that make it hard to visualize the larynx or partially or completely obstruct the upper airway. Examples include: history of previous problems with anesthesia or sedation including prolonged intubation or unplanned hospitalization, stridor, snoring, or sleep apnea, chromosomal abnormality (e.g., Trisomy 21), history of prematurity with prolonged intubation, significant obesity, short neck or limited neck mobility, receding mandible (small lower jaw) or decreased hyoid-mental distance, dysmorphic facial features (e.g., Pierre–Robin syndrome), small mouth opening, protruding incisors, loose teeth, dental appliances, high, arched and narrow palate or history of cleft palate repair, large tongue, tonsillar hypertrophy, or no visible uvula (Fig. 15.1 Mallampati airway classification III, IV) [69, 70].

Problems associated with increased risk of adverse events and for which consultation

Table 15.1 ASA physical status-E classification [71]

Status	Disease state
I	No organic, physiologic, biochemical, or psychiatric disturbance
II	Mild to moderate systemic disturbance that may or may not be related to the reason for procedure, e.g., *mild asthma, well-controlled diabetes, controlled seizure disorder, anemia*
III[a]	Severe systemic disturbance that may or may not be related to the reason for procedure, e.g., *heart disease that limits activity, poorly controlled essential hypertension, diabetes mellitus with complications, chronic pulmonary disease that limits activity, poorly controlled seizure disorder*
IV[b]	Severe systemic disturbance that is life-threatening with or without procedure, e.g., *advanced cardiac, pulmonary, renal, endocrine or hepatic dysfunction, e.g., severe bronchopulmonary dysplasia, sepsis*
V[b]	Moribund patient who has little chance of survival but is submitted to procedure as a last resort (resuscitative effort), *e.g., septic shock, cerebral trauma, pulmonary embolus*

"E" is added to indicate a nonelective or emergent procedure, e.g., ASA I–E

[a] Consultation with experienced sedation provider or anesthesiologist encouraged

[b] Consultation with anesthesiologist strongly encouraged

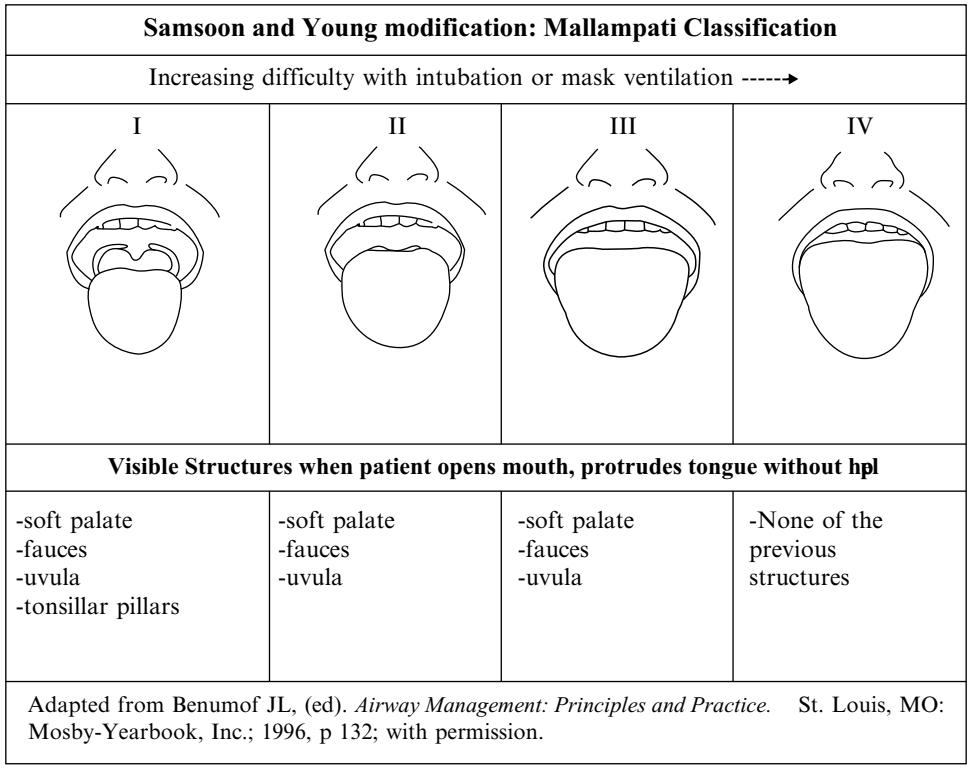

Fig. 15.1 Mallampati airway classification (adapted from Benumof [360]; with permission)

with an experienced sedation practitioner or anesthesiologist is suggested include: [74]

- ASA physical status III or IV
- Current upper respiratory illness (URI)[1]
- Pulmonary: wheezing not cleared by a bronchodilator, obstructive sleep apnea
- Morbid obesity (>2× ideal body weight)
- Cardiovascular conditions: cyanosis, congestive heart failure
- Neurological conditions: poorly controlled seizures, central apnea
- Gastrointestinal conditions: uncontrolled gastroesophageal reflux
- Prematurity with residual pulmonary, cardiovascular, gastrointestinal, neurological problems
- Age <3 months
- Pregnancy or suspected pregnancy
- Neuromuscular disease
- Severe developmental delay
- Patients who are difficult to control
- History of failed sedation, over-sedation, or paradoxical response to sedatives

Screening for acute illness: Patients should be screened for acute illnesses that may increase their risk for sedation-related adverse effects. When acute illness is detected, the sedation provider must weigh the increased risk against the need for the diagnostic or therapeutic procedure.

(c) *Fasting status and risk of aspiration*. To decrease the risk of pulmonary aspiration of gastric contents in healthy children undergoing general anesthesia for elective

[1] Note: Upper respiratory illness (URI) may increase the risk of laryngospasm, bronchospasm, and hypoxia during sedation. Mild URI symptoms alone (non-purulent rhinitis, afebrile, cough that clears) may not be an indication to cancel PSA but management should reflect anticipation of above potential complications. Severe URI (febrile, purulent discharge, wet cough) should prompt consideration of cancelation of non-emergent or urgent procedures.

procedures, fasting from clear liquids a minimum of 2 h and from milk or solid food 6–8 h is a well established consensus-based practice [75]. However, as noted in these guidelines, "Published evidence is silent on the relationship between fasting times, gastric volume, or gastric acidity and the risk of emesis/reflux or pulmonary aspiration in humans." In two more recent reviews of the literature examining whether children should undergo fasting prior to ED PSA [76, 77], it is noted that little clinical data has been published to help answer this question. It is difficult to extrapolate directly to PSA from the long experience with safe general anesthesia. It is likely that risk of aspiration is less during ED PSA compared to general anesthesia in the operating room for several reasons. First, protective airway reflexes are generally preserved at the depth of moderate sedation [69, 78]. Second, airway reflexes are also relatively intact during sedation with the commonly used dissociative agent ketamine during deep sedation or even light general anesthesia [79]. Of concern, however, these reflexes are likely blunted during deep sedation with opioids, benzodiazepines, barbiturates, propofol, and etomidate, especially if sedation is deep enough to cause apnea [77]. Third, intubation of the trachea, rarely performed in children undergoing ED PSA, likely increases the risk of pulmonary aspiration due to pharmacological abolition of protective reflexes to facilitate intubation and mechanical interference with these reflexes during passage of the endotracheal tube into the trachea [72, 73, 80]. Fourth, the great majority of children receiving ED PSA meet ASA physical status class I or II criteria [9, 61–63, 78, 81] and, compared to those in ASA physical status classes III and IV, are associated with less risk of adverse events during anesthesia [72, 73]. It is the combination of these differences, i.e., moderate sedation, common use of dissociative ketamine for deep sedation, lack of manipulation of the larynx, and healthy patients, that likely results in ED PSA having lower risk of aspiration compared to general anesthesia.

A more robust literature on identification of risk factors for aspiration in children undergoing general anesthesia has found no benefit from routine preoperative administration of antacids or pharmacological agents to increase gastric motility [75, 82]. Gastric fluid volume or pH were not different with NPO periods of 2, 4, and 12 h after drinking apple juice in one study [83] or after 30 min to 3 h, 3–8 h, or more than 8 h after clear liquid ingestion in another trial [84]. No studies have examined gastric emptying in children after solid intake but one small study of adult women after a light breakfast found 3 of 8 had emptied their stomachs by 2 h and all by 6 h [85].

The incidence of pulmonary aspiration during ED PSA is uncertain but appears to be very low. In a literature review of adverse events during ED PSA [76], after combining studies with a total of 4,814 children, clinically apparent aspiration during PSA was reported in only 1 account of 2 children, both of whom had fasted standard NPO periods and did not appear to be ED patients. These patients were deeply sedated with opioid-barbiturate combinations which blunt airway reflexes, one for a radiological procedure and the other for bronchoscopy. Both required only supplemental oxygen and observation [68]. In nearly 50,000 elective propofol-based sedations, 4 children were noted to have aspirated; all recovered without sequelae after positive-pressure ventilation and supplemental oxygen, and were discharged the day of or day after the procedure [86]. The incidence of aspiration in more than 100,000 children undergoing general anesthesia has been reported to be 1:978 and 1:2,632 patients by Warner [72] and Borland [73]. During emergency surgery, aspiration occurred as frequently as 1:373 patients in the Warner study [72]. Although only a rough estimate, pooling of the available data in the literature

suggests the incidence of clinically apparent pulmonary aspiration during ED PSA is no more frequent than 1:2,000 pediatric patient encounters [76]. Because of the rarity of its occurrence, much larger studies are needed to accurately estimate the incidence of aspiration, and any relationship with fasting, during ED PSA. For now, given the many variables present, clinical judgment has to weigh the risk and benefits for each patient [76, 77].

Vomiting, although not likely to result in aspiration when protective airway reflexes are intact, is a common adverse event during ED PSA in children, occurring in as much as 25% of patients, especially when opioids are coadministered prior to sedation [87, 88]. As supported by literature reviews [76, 77, 89], recent series of children receiving ketamine or nitrous oxide for ED PSA suggest there is poor correlation between the length of time of preprocedural fasting and vomiting [62, 63, 90]. No significant difference in frequency of vomiting was found between children fasted between 0, 2, 4, 6, 8, and greater than 8 h. This may be because the vomiting is medication induced and gastric contents have little effect on likelihood of vomiting.

Gastric emptying may also be unpredictably delayed in ill or injured patients due to development of ileus [91]. ED management of pain with opioids likely exacerbates this problem. Whether brief delay (1–6 h) of PSA decreases vomiting is undetermined. Coadministration of ondansetron has been found to reduce vomiting associated with ketamine-based ED PSA but only from 12.6 to 4.7% with 13 patients needing to be treated to prevent one episode of vomiting [92]. This and other strategies need further investigation. It is the practice of the author to consider all sedated ED patients to have "full stomachs" and to manage them with vigilance and preparation for assisting them in clearing their oropharynx by rolling them to their side or assisting them in leaning forward. Suctioning of the mouth is then used, if needed, to "mop up."

Pregnancy: Since many medications administered for ED PSA have the potential for causing harm to a fetus, it is recommended that the menstrual status be reviewed with post-menarchal girls and a urine pregnancy test performed prior to sedation. The United States Food and Drug Administration (FDA) has categorized medications based upon known or possible risk to a developing fetus as listed in Table 15.2. Increasing uterine size, greater tendency for vomiting, and many other changes also increase the complexity of PSA during pregnancy.

Table 15.2 United States FDA pharmaceutical pregnancy categories

Category A	Adequate studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters
Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester
Category C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
Category D	There is a positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
Category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

2. Informed consent
   The physician responsible for the sedation should provide to the patient and/or parents information concerning the objectives of the sedation, behavioral changes associated with the sedative regimen (especially important when the parent/guardian plans to remain with the patient during the sedation/procedure) and potential adverse effects during and after the sedation [59, 69, 93]. Parents should understand that, albeit rare, there is a risk of pulmonary aspiration, cardiopulmonary compromise, hypoxic brain injury, and/or death. *It is also recommended to discuss with them the possible need for muscle relaxation, intubation, hospitalization, and unsuccessful sedation with inability to perform the procedure*. These issues that have been discussed with the parent/guardian (and patient when appropriate) and that they have given their informed consent to proceed with the sedation, should be documented on the sedation record.

   Adverse effects/events generally discussed include:
   - Incomplete analgesia and/or amnesia
   - Respiratory depression/apnea
   - Pulmonary aspiration
   - Psychosis, recovery dysphoria
   - Catatonia/nystagmus
   - Dysrhythmias
3. Plan for sedation
   (a) *Selection of a medication plan*. Selection of medications and dosages should be guided by the desired key effect(s). An ideal regimen would provide acceptable analgesia, sedation and amnesia for residual awareness of procedure-related pain or anxiety, cause minimal adverse effects and work reliably with a wide therapeutic index, i.e., small differences in dose would not cause over-sedation or adverse events, have rapid onset and recovery, and be easy to titrate to effect. No single agent or combination of agents fully achieves these goals. Selection of procedural sedation medications therefore is based upon balancing desired effects with the potential for adverse effects. For procedures that are very painful, e.g., fracture reduction, control of the pain will be paramount. For procedures that require the child to be motionless, e.g., computerized tomography (CT) or magnetic resonance imaging (MRI) scans, immobility may be most important. Most procedures in children require some combination of analgesia and immobility along with anxiolysis, therefore sedation planning can be broadly organized into categories of these parameters.

Analgesia, hypnosis, anxiolysis or amnesia? Balanced sedation: Medication selection and dose can be organized by anticipation of whether the procedure is: (1) nonpainful/noninvasive, or associated with (2) low level of pain and high anxiety or (3) high level of pain, high anxiety, or both, (4) whether local anesthesia can be used, and (5) whether the patient needs to be motionless, i.e., for some procedures, some motion is acceptable during painful and/or invasive procedures to the extent that the motion neither causes risk to the patient nor hinders the successful performance of the procedure, whereas in others, e.g., MRI, any movement prevents completing the procedure (see Table 15.3) [61, 94, 95].

Principle and secondary effects of sedative/analgesic medications are summarized in Table 15.4. Although combining sedative/analgesic medications generally increases the risks of adverse effects [96, 97], the actual depth of sedation is likely to be a better predictor of these risks [94, 98]. Thoughtful "balanced sedation" with anxiolytic and analgesic drugs, carefully titrated to effect, can achieve very satisfactory sedation and typically results in smaller effective doses of individual drugs than if a single drug is used. For example, fentanyl is a potent analgesic but has little or no anxiolytic or amnestic effect, whereas midazolam is a potent anxiolytic and amnestic agent with no analgesic effect. Combining fentanyl and midazolam results in effective procedural sedation but the combination causes significantly greater respiratory depression than either fentanyl or midazolam alone [96].

Table 15.3 Indications and strategies for procedural sedation and analgesia [94, 95]

Pain	Anxiety	Motion	Clinical examples	Suggestion sedation strategies
No	Moderate	Some acceptable	Echo, EEG, Infant PFTs (sedation rarely needed)	Comforting, distraction Chloral hydrate PO (in patients <2 year of age) Midazolam PO
		Motionless	Computed tomography Magnetic resonance	Chloral hydrate PO (in patients <6 months of age) Pentobarbital ± Midazolam IV Propofol IV
Low or local anesthesia can be used	Moderate to high	Relatively motionless but some acceptable	Abscess incision and drainage Dental procedures, lumbar puncture Flexible fiberoptic laryngoscopy Ocular irrigation Foreign-body removal Phlebotomy, IV cannulation Laceration repair, simple Fracture reduction with hematoma block Paraphimosis reduction Sexual-assault examination	Topical or local anesthesia Comforting, distraction Oxycodone PO Nitrous oxide Midazolam PO, PR, IN, IV
High	Moderate to high	Relatively motionless but some acceptable	Abscess incision and drainage Arthrocentesis Bone marrow aspiration Burn débridement Cardioversion Foreign-body removal Complicated Fracture or dislocation reduction Hernia reduction Laceration repair, complex Paracentesis Thoracentesis Thoracostomy-tube placement	Midazolam and Fentanyl IV Ketamine IM or IV Nitrous oxide and oxycodone PO Propofol and ketamine or fentanyl IV

Table 15.4 Procedural sedation medication effects

Medication	Sedation	Analgesia	Amnesia	Anxiolysis	Emetogenic
Barbiturates	+++	–	–	–	
Benzodiazepines	+++	–	+++	+++	Antiemetogenic
Fentanyl	+	+++	–		++
Ketamine	+++	+++	++		+
Propofol	+++	–	+	+	Antiemetogenic
Chloral hydrate	++	–	–		
Nitrous oxide	++	++	+++	+++	++

Depth of sedation: Since increasing depth of sedation is associated with increasing frequency of adverse events [94, 99], use of the lightest effective sedation is usually preferred. However, frequently the depth of sedation required for a particular procedure cannot be accurately predicted in a specific patient [94]. Incompletely appreciated anxiety and lack of comprehension in younger children or those with developmental delay often cause need for deeper than anticipated sedation for procedures in which local anesthesia or mild sedation would suffice in a self-controlled adolescent or adult. For intensely painful procedures, deep sedation is typically required. Clinicians providing sedation, therefore, ideally should be trained and prepared to administer increasingly deeper sedation as guided by the patient's response to the procedure. It is important, too, for the clinician to realize that many sedative analgesic agents also induce varying degrees of amnesia. When midazolam, ketamine, or propofol, and to a lesser extent nitrous oxide, are administered, the patient is unlikely to recall clearly procedure-related pain despite occasional moaning or crying out during intensely painful parts of the procedure [9]. However, it is unwise to promise complete amnesia during the informed consent process. The extent of procedural amnesia can be assessed in part by asking the patient if he/she "recalls anything hurting" after they have recovered; a negative answer is reassuring to parents who have remained with the patient during the procedure. Because of amnesia for procedure-related pain, lighter and presumably safer levels of sedation may be acceptable when patient motion does not interfere with accomplishment of the procedure. For this reason, the amnestic agent midazolam is combined with fentanyl for PSA because completely effective analgesia cannot be achieved with fentanyl without marked respiratory depression. Of note, deeper sedation with ketamine is usually much less associated with adverse cardiopulmonary effects in comparison to other agents and, in addition, ketamine induces moderate amnesia.

Some older children may prefer not to be deeply sedated, in the same way many adults fear general anesthesia. As an example, a 13-year-old boy sedated by the author with nitrous oxide in conjunction with a lidocaine fracture hematoma block, recalled the next day the details of the reduction of his displaced distal radius and ulnar fractures. Yet, he was adamant that he would not have preferred to have been "put to sleep" and unaware of the reduction. Since the hematoma block was very effective and he recalled no pain, he was very satisfied with his experience of altered awareness during the fracture reduction. When local anesthesia or other analgesic technique can be achieved, some children may prefer lighter levels of sedation without loss of awareness, a concept that needs further investigation.

(b) Staffing

For moderate sedation, a sedation provider trained in the sedation protocol and skilled in pediatric advanced life-support techniques is responsible for the procedural sedation-analgesia, including monitoring of the patient's status. In the ED, this is typically the emergency physician. If, after induction of adequate sedation, that individual then performs the procedure for which sedation is provided, a second individual,

typically a registered nurse, with sedation training and knowledgeable in pediatric basic life-support must be at the bedside and responsible for monitoring the patient's cardiopulmonary status and the need for interventions to manage adverse events. This second individual often is responsible for recording the patient's status on the Sedation Record and may assist with minor, interruptible tasks once the patient's level of sedation and cardiopulmonary functions have stabilized, provided that adequate monitoring of the patient is maintained [59, 67, 69, 100].

For deep sedation in the ED, a sedation provider, again, typically the emergency physician, with training in the pharmacology of the agents to be administered and skilled in pediatric advanced life-support must be in the procedure room and is responsible for the procedural sedation-analgesia, including monitoring of the patient's status. At least one clinician must be assigned to monitor and record the patient's airway patency and cardiorespiratory status and, in contrast to moderate sedation planning, should have no other responsibilities during induction of sedation, the procedure and the early postprocedure period when the patient is at greatest risk for respiratory depression, partial upper airway obstruction, and aspiration. If an experienced sedation provider has induced adequate sedation and will then perform the procedure, primary responsibility for monitoring the patient's cardiopulmonary status may be designated to a second sedation trained clinician, typically a registered nurse, if the responsible provider can easily interrupt performance of the procedure to assist with or assume management of adverse events. It should not be planned that the clinician monitoring the patient would assist with the procedure as that may distract this clinician from monitoring the patient's vital signs and clinical status or interfere with rapid intervention [59, 67, 69, 100, 101]. Brief, interruptible assistance with the procedure may be provided by this person but with caution and with assured concurrent attention to the patient's vital functions. Safe use of deep sedation is dependent upon this clinician's meticulous attention to the patient's airway and breathing and anticipation and early recognition of adverse events. Threats to ventilation and oxygenation usually are easily managed when rapidly recognized and interventions immediately implemented. Experience with deep sedation has shown that some patients (~5–25%) will develop oxygen desaturation of <90% and partial upper airway obstruction, both of which are usually easily managed when rapidly recognized.

Since deeper than intended sedation may occur or be necessary in any patient, it is recommended that all but the lightest sedations, e.g., use of nitrous oxide, be staffed and monitored as if deep sedation may occur, particularly when gaining initial experience with sedation protocols or using agents with narrow therapeutic indices, e.g., propofol, midazolam + fentanyl, or etomidate. This usually means a third provider is needed if assistance will be necessary in performing the procedure. In addition, at least one provider should be present who is intimately familiar with location of resuscitation and other necessary medical equipment.

In most hospitals, physician sedation providers and nurses must be credentialed to administer PSA. Credentialing typically includes didactic sessions on use of specific PSA medications, demonstration of safe and effective administration of PSA, and competency in skills needed for rescue from adverse events [93].

(c) Monitoring and equipment

Direct patient observation: In addition to electrophysiological monitoring, airway patency, rate and depth of respiration, and the child's color (nail-beds, mucosa) should be checked frequently by vigilant direct observation, especially after each medication administration and in the early postprocedure period when painful procedural stimuli

have ended. This enables essential immediate interventions for adverse events such as marked respiratory depression, positional obstruction of the upper airway as muscle relaxation occurs (snoring, paradoxical chest wall motion without exhaled breaths may be noted), or vomiting. Opening of the airway by realignment or jaw thrust, applying painful stimulation to awaken and induce breathing, administering supplemental oxygen, or turning and suctioning to clear vomit often are usually all that is needed to correct problems that can otherwise rapidly deteriorate to life-threatening situations.

Direct monitoring during recovery should continue by a designated healthcare provider until the patient emerges to a level of moderate sedation; thereafter direct monitoring can be designated to the child's parent or another responsible adult with the healthcare provider immediately available until the patient returns to the pre-sedation level of responsiveness [59, 67, 100, 101].

Patients undergoing sedation should wear a loose fitting top or hospital gown to ensure easy direct observation of the chest. The patient's mouth and nose should not be obscured and skin should be visible for monitoring of color. A stethoscope should be immediately available.

For *moderate sedation*, in addition to direct observation, measurement of oxygen saturation by pulse oximetry is strongly recommended [59, 67, 100, 101]. Additional continuous electrophysiological monitoring throughout sedation and recovery of ECG-based heart rates, respiratory rates, and noninvasive automated blood pressures measured after each medication bolus and/or every 5 min add further measures of safety.

For *deep sedation*, in addition to direct observation, routine use of noninvasive physiologic monitoring should include continuously measured oxygen saturation, heart rate, and respiratory rate, and, in addition, noninvasive automated blood pressure measurements after each medication bolus and/or every 5 min throughout sedation and recovery [59, 67, 100, 101].

Pulse oximetry has been demonstrated to detect hypoxemia well before cyanosis occurs and is therefore critical for monitoring for respiratory compromise. In one study of infants, O_2 saturations were ≤83% before perioral cyanosis was detected by experienced emergency pediatricians [102]. Monitoring of oxygen saturation with pulse oximetry has been suggested as the most important means of reducing sedation related injury and should be used for all but minimal sedations [59, 67, 69, 98, 100, 101]. The *pulse oximeter audible tone should be activated* to alert providers to changes without the need to frequently read the monitor instead of observing the patient.

End-tidal CO_2 capnography provides breath-to-breath information on the effectiveness of ventilation and is increasingly being investigated in patients undergoing ED PSA. Assessment of ventilation by continuous end-tidal CO_2 capnography has been found more sensitive than either direct observation or decreases in oxygen saturation in detecting respiratory depression or airway obstruction. Changes in capnographic wave form and/or changes in end-tidal CO_2 are frequently noted well before changes in oxygen saturation, including in patients breathing room air [103–109]. Of note, no changes in end-tidal CO_2 were found in children sedated with ketamine alone [110, 111]. Changes in end-tidal CO_2 capnography can aid in early recognition of respiratory depression and/or airway obstruction and allow initial interventions that may avert the need to administer positive-pressure ventilations, e.g., limitation of further administration of sedative medications or opening of the airway. Assisted ventilation during oxygen desaturation due to apnea or periods of respiratory depression should be administered as needed. However, positive-pressure ventilation increases gastric pressures due to insufflation of air into the stomach. At a depth of sedation that induces apnea or significant respiratory depression, there is likely concurrent relaxation of esophageal muscle tone and significant blunting of protective airway reflexes. Thus, there is likely increased risk of pulmonary aspiration associated with positive-pressure ventilation due to gastroesophageal reflux into the oropharynx.

Routine administration of supplemental oxygen has been recommended to prevent hypoxemia during deep and moderate sedation [101]. However, sedation providers should recognize that administration of supplemental oxygen may

delay oxygen desaturation for several minutes during respiratory depression or apnea [112]. Therefore, use of supplemental oxygen may delay recognition of these adverse events with their likely concurrent depression of protective airway reflexes, unless the patient is also monitored by end-tidal CO_2 with capnography [113]. Similarly, recognition of airway obstruction is likely delayed [103–106, 108, 110, 114]. When capnography is unavailable, consideration should be given to monitoring patients by pulse oximetry as they breathe room air. Although an indirect and less sensitive measure of ventilation than capnography, decreases in oxygen saturation alert the clinician to decreases in ventilation and facilitate interventions before hypoxemia and a need for positive-pressure ventilation occurs. With this strategy, administration of supplemental oxygen may be reserved for patients whose oxygen saturations drop below 90% without rapid rise in response to airway maneuvers such as head tilt/jaw thrust and/or stimulation. Respiratory depression is sufficiently commonplace during sedation with propofol that many providers recommend as routine administration of supplemental oxygen during propofol PSA [105, 106, 115].

Equipment

Resuscitation equipment must be immediately available. A self-inflating (Ambu-type) bag-mask positive-pressure device with a PEEP attachment and appropriately sized mask, continuous oxygen supply, and an airway suctioning device with a large rigid suction tip should be prepared for each sedation. Anesthesia style CPAP bags, endotracheal intubation equipment, and resuscitation medications, with a dosing guide, including reversal agents such as naloxone and flumazenil, a paralytic agent such as succinylcholine, and antiepileptic and antiarrhythmic medications for drug induced seizures and dysrhythmias should be immediately available for all sedations [59, 67, 69, 100, 101].

No suction apparatus can clear the oropharynx during active vomiting. The patient must be helped to turn or roll to the side or to sit upright to clear his airway. The suction device is used to clear residual emesis from the mouth after active vomiting has stopped. If the patient is unresponsive and emesis is noticed in the posterior pharynx or mouth, the patient should be rapidly rolled to the side to allow emesis to passively flow out as suctioning of the posterior pharynx is performed; there is significant risk for pulmonary aspiration in this situation.

Intravenous access adds an additional invasive procedure to the patient's treatment, but it enables easily controlled and rapid titration of medications and provides an increased margin of safety by enabling rapid administration of reversal and resuscitation agents, if needed. When medications are administered intravenously, the intravenous access should be maintained throughout sedation and recovery. When medications are administered by a non-intravenous route, e.g., by intramuscular injection, whether to establish intravenous access should be decided on an individual basis. If vascular access is not established, the ability to immediately accomplish such must exist for all sedations, especially when a multiple drug sedation regimen is used. For agents that frequently cause hypotension, e.g., propofol, it is recommended that intravenous access be established with an indwelling catheter and maintained with a resuscitation fluid (lactated Ringer's solution or normal saline). Patients who have been NPO for an extended period may benefit from an infusion of 10–20 mL/kg of LR or NS to counter any hypotensive effects of sedation medications. A stopcock near the hub of the IV catheter, e.g., on the tail of a T-connector inserted into the hub of the catheter and in-line with the IV fluids, facilitates controlled and complete administration of sedation medications. This setup allows a syringe containing the sedative to be connected to the stopcock and the medication injected near the hub as the IV fluids infuse. This reduces the possibility of uncertain medication infusion amount and rate that might occur if the medication is added considerably upstream of the catheter hub. For agents such as ketamine that do not frequently cause hypotension, an indwelling "saline lock" is typically sufficient; the ketamine can be flushed into the bloodstream with 5–10 mL boluses of saline following ketamine administration.

A mnemonic some find helpful to summarize equipment preparation is MS-MAID: Machine Suction – Monitors Airway (oral airway, bag-mask, ETT, blade) IV Drugs.

Preparation for and Management of Adverse Events

Anticipation

The rarity of serious adverse events in ED PSA can lull the provider into complacency [116, 117]. It is suggested the possibility of a life-threatening event during PSA should be thought of as inevitable, as a matter of "when" rather than "if." Since these events are so infrequent and variations in individuals' responses to a medication are not always predictable, the provider must always be prepared.

Effective management of adverse events begins first and foremost with preparation for the planned sedation. Thorough pre-sedation evaluation to identify patients at increased risk for adverse events or difficult airway management, monitoring and staffing based upon intended sedation depth, and immediate availability of resuscitation equipment and medications are critical. Factors associated with serious adverse outcomes include late recognition of hypoxemia and inadequate resuscitation, thus emphasizing the importance of preparation and continual monitoring during the sedation and recovery periods [98]. If recognized early, most adverse effects can be addressed effectively with relatively minor interventions. Stimulation, airway realignment, jaw thrust, and supplemental oxygen are usually all that is needed to avoid further deterioration to life-threatening events [117].

Management of Respiratory Depression and Apnea

Respiratory depression is one of the most common potentially serious effects of pediatric PSA [66, 116, 117]. A critical incident analysis of serious adverse outcomes in pediatric sedation found 80% initially presented with respiratory depression [98]. Widespread use of pulse oximetry has since dramatically improved early recognition of respiratory depression. Agents commonly associated with respiratory depression include the sedative-hypnotics (barbiturates, benzodiazepines, chloral hydrate, propofol), particularly when used in conjunction with opioids [99, 118]. Apnea has also been rarely reported with administration of ketamine [119–121].

Avoiding respiratory depression: (see also basic pharmacokinetics) Most sedative medications variably blunt brainstem receptor response to increases in plasma levels of CO_2. Since response to rising levels of CO_2 determines breathing rate and depth, significant increases in sedative concentrations in the brainstem quickly lead to respiratory depression or apnea. The more rapidly a sedative drug is infused, the higher its initial brainstem concentration and the greater the respiratory depression. A primary strategy for reducing respiratory depression and maintaining adequate ventilation (and, in association, oxygenation) is slow administration of PSA drugs, often achieved by repeatedly infusing half or less of the total expected dose until the desired effect is achieved (titration). Ketamine can be an exception to the recommended slow administration approach because of its unique relative lack of respiratory depression. Taking advantage of first-pass kinetics, experienced sedators may choose to administer smaller doses rapidly for very brief procedures (see Section "Ketamine").

At risk periods: Patients may experience respiratory depression at any time during the sedation, but the greatest risks are immediately after medication administration and again after cessation of painful procedural stimuli [122].

Recognition of ineffective ventilation: As detailed previously, direction observation of the patient including general color and chest wall movement continues to be one of the most important means of recognizing respiratory depression and/or airway obstruction. The patient's oropharynx and chest wall should be directly visible at all times to facilitate observation for lack of respiratory effort, or respiratory effort without air exchange. In addition, *pulse oximetry with audible tone*, and *end-tidal capnography* facilitate detection of ventilatory changes before they are clinically apparent.

Airway and Ventilation Maintenance

Initial management of hypoventilation may simply require *verbal encouragement* to the patient *to breathe* as their sensitivity to rising CO_2 has been blunted by the sedation medications. Patients who have received opioids such as fentanyl may be awake but "forget" to breathe. *Stimulation*, painful

if necessary, to arouse the patient may improve muscle tone and prompt breathing. If oxygen saturations are falling despite these maneuvers, supplemental oxygen administration and airway opening maneuvers and/or positive-pressure ventilation may be necessary. See section below for management of upper airway obstruction.

Treatment: Respiratory Depression and Apnea

When monitors alarm, e.g., indicating dropping oxygen saturation, ASSESS THE PATIENT. DO NOT presume the pulse oximeter probe has slipped off, monitor malfunction, etc. Evaluate equipment later!

First Line: (in Rapid Succession, If Needed)

1. Verbally encourage or stimulate patient to breathe deeply (patients may require intensely painful stimuli, e.g., squeezing the fracture site or a hard sternal rub with knuckles); if insufficient then
2. Support airway (chin lift/jaw thrust); if insufficient then
3. Administer supplemental oxygen
4. If spontaneous ventilation continues to be inadequate, administer positive-pressure ventilation via bag/mask
5. If patient is on a continuous infusion (e.g., propofol) – slow down or stop medication infusion, then
6. Call for help, if needed

Second Line: Reversal Medications for Opioids and Benzodiazepines

If respiratory depression occurs after administration of an opioid or benzodiazepine and does not readily resolve after the above supportive measures, or requires continued positive-pressure ventilation, consider use of reversal agents. *Slow, titrated reversal* is preferred if positive-pressure ventilation is effective. The desired endpoint is lessening of the respiratory depression with slightly lighter sedation. Rapid, full reversal may lead to severe pain, hypertension, and agitation or seizure [123]. Reversal agents are rarely needed by experienced sedation providers.

Naloxone (Narcan®)

Indications: Opioid-induced apnea, respiratory depression, or "wooden/rigid chest syndrome" not responding to stimulation, airway opening maneuvers, supplemental oxygen, and/or positive-pressure ventilations.

Dose: 1–2 μg/kg (0.001–0.002 mg/kg) *IV push* repeated every 1–3 min until the patient begins to have spontaneous respirations. Doses of 1–2 μg/kg are recommended to "gently" reverse opioid-induced respiratory depression yet maintain analgesia. Larger doses, such as 10–100 μg/kg may awaken the patient and reverse the analgesic effects resulting in significant pain, hypertension, pulmonary edema, vomiting, or seizures [123].

During the interval of apnea, the patient is supported with assisted ventilations until adequate spontaneous respirations are restored. Thereafter, the patient is observed closely as the reversal effects of naloxone may be briefer than the opioid-induced respiratory depression. For "wooden chest syndrome," if the patient cannot be ventilated and oxygen saturations are dropping rapidly, naloxone may be given in 1 or 2 mg boluses for convenience. Alternatively, succinylcholine 1–2 mg/kg may be used to paralyze the patient.

Caution: opioid-induced respiratory effects may outlast the duration of naloxone and patients must be closely monitored for recurrence of respiratory depression, typically at least 2 h after naloxone administration [124].

Flumazenil (Romazicon®)

Indications: Benzodiazepine (e.g., Midazolam) induced apnea or respiratory depression not responding to stimulation, airway opening maneuvers, supplemental oxygen, and/or positive-pressure ventilation.

Dose: 0.01–0.04 mg/kg (maximum 0.5 mg) IV over 30 s. Repeat every 60 s to desired response. A cumulative dose of 3 mg may be necessary. Flumazenil may reverse midazolam-induced hypnotic and amnesic effects but may not reverse ventilatory depression [125]. When appropriate, naloxone should be used as the first line in reversal therapy. Drug therapy does not obviate the need to protect the airway and support ventilation.

Table 15.5 Naloxone & Flumazenil for reversal of respiratory depression [127]

Agent	Route	Dose	Frequency	Maximum dose (mg)	Onset	Duration (min)
Naloxone	IV, IM, or SC	1–2 μg/kg for respiratory depression 100 μg/kg (0.1 mg/kg) if unable to ventilate or *wooden chest*	Q 2–3 min as needed	2	1–2 min (IV) 15 min (IM/SC)	30–60
Flumazenil	IV	10 μg/kg (0.01 mg/kg)	Q 1 min as needed	1[a]	1–2 min, maximum effect 6–10 min	20–60

[a]If resedation after response to Flumazenil, additional doses of up to 1 mg/dose may be given q 20 min to a maximum total dose of 3 mg

Caution: Flumazenil may cause seizures in patients chronically on benzodiazepine medications and should be used cautiously in patients on medications that can lower seizure threshold. Also, benzodiazepine induced respiratory effects may outlast the duration of flumazenil and patients must be closely monitored for recurrence of respiratory depression, typically at least 2 h after flumazenil administration [126, 127]. Recurrence of sedation has been reported in up to 7% of cases, most commonly in children under 5 years of age [126] (Table 15.5).

Upper Airway Obstruction

The pediatric airway is particularly prone to dynamic obstruction due to the relatively large size of the tongue and tonsillar tissues. As sedation depth increases, the muscles of the tongue, jaw, and oropharynx loose tone in a manner similar to deep sleep. Sedation-induced "obstructive sleep apnea" may result in partial or complete airway obstruction, exacerbated by the supine position and nasal passage obstruction. A history of snoring or obstructive sleep apnea alerts the clinician to the increased likelihood of this occurrence. Placement of a shoulder roll in infants and a head roll in older children and adolescents to align the oropharynx, posterior pharynx, and trachea may help align the patient's airway and relieve this obstruction. Markedly, obese patients also may benefit from a large head or shoulder roll to compensate for their large trunk.

A jaw thrust or chin lift may be necessary to open the upper airway by pulling the tongue and related muscles away from the posterior pharynx. Patients who are very deeply sedated or have inadvertently reached the depth of general anesthesia may benefit from placement of an oro- or nasopharyngeal airway but because oropharyngeal airways may induce a gag reflex and vomiting, these devices should be used with caution. Laryngospasm is a special type of upper airway obstruction and is addressed below.

At risk periods: Positional airway obstruction may occur at any time during sedation but, in association with respiratory depression, it may more likely be shortly after medication administration or after the painful procedural stimulus has ended. Ketamine-related laryngospasm may occur in settings of current URI, unsuctioned secretions/vomitus, or stimulation of the hyperactive gag reflex during a procedure.

Recognition of upper airway obstruction: Signs of partial upper airway obstruction include stridor or noisy breathing. Paradoxical chest wall movement (sucking in of the chest and distention of the abdomen with inspiration) may be seen with partial or complete obstruction. Hypoxemia is a late sign. An obstructive pattern is seen on capnography well before changes in oxygen saturation and allows early detection of airway obstruction (or apnea).

Treatment

1. Align airway and open with chin lift or jaw thrust; provide supplemental oxygen as needed.
2. Suction airway if excessive secretions are present.

3. If not responding to repositioning, consider continuous positive airway pressure (CPAP) with bag/mask (CPAP or anesthesia type bag is preferable to self inflating-type bag as CPAP can be delivered more effectively to open the airway by distending the posterior pharynx).
4. If having difficulty maintaining an open airway, consider an oral airway (unconscious patient), or nasal airway.
5. If unable to ventilate with CPAP, rapidly consider treatment for laryngospasm with *succinylcholine*.

Laryngospasm

Laryngospasm is an uncommon but *potentially life-threatening* sedation related adverse event. It is a partial or complete upper airway obstruction, with oxygen desaturation, caused by involuntary and sustained closure of the vocal cords and is not relieved by routine airway repositioning maneuvers, suctioning, or insertion of a nasal or oral airway. Laryngospasm may be intermittent or sustained, brief or prolonged [132, 133].

The incidence of laryngospasm during pediatric ED PSA is difficult to determine as it is a rare event and large sedation databases are not available for estimation. Relative preservation of upper airway protective reflexes during ketamine-based sedation reduces the risk of pulmonary aspiration and thus makes ketamine one of the safest agents for ED PSA in unfasted children, yet, paradoxically, ketamine PSA may have increased risk for laryngospasm [134–136]. A meta-analysis of pediatric ketamine-based ED PSA found an incidence of laryngospasm of 0.3%; the only identifiable association with increased risk of laryngospasm was an initial intravenous dose of greater than 2.5 mg/kg but data was unable to be analyzed for associations with URI, wheezing, or other risk factors found to be associated with increased risk during general anesthesia [137]. Of particular interest, young age and oropharyngeal procedures (excluding endoscopy) were not associated with increased risk but prospective larger data sets are needed to better clarify these risks.

Laryngospasm in almost 50,000 non-intubated children undergoing elective propofol sedation/anesthesia was noted to occur at a rate of 21/10,000 (0.2%) [86]. Laryngospasm associated with general anesthesia has been estimated as high as 14% in younger children and as low as 0.1%, with lower likelihood reported in non-intubated children [138, 139]. The wide variability may be due to differences in definition and study design, patient populations, anesthetic techniques, and airway manipulation [140]. However, consistently noted risk factors for laryngospasm include young age, upper respiratory infection, asthma, manipulation of the airway, and exposure to smoking in the home [141, 142].

It is unclear whether prophylactic administration of atropine or glycopyrrolate with ketamine to reduce hypersalivation reduces the risk of laryngospasm [143, 144]. The meta-analysis of pediatric ketamine-based ED PSA, noted earlier, found that overall airway and respiratory adverse events (but not laryngospasm) were actually increased in children who received concurrent anticholinergics; [137] this unexpected association needs further investigation.

At risk periods: Laryngospasm may occur at any time during sedation, including recovery. In one report of non-intubated children undergoing sedation/general anesthesia, laryngospasm occurred most frequently during emergence (48%), but was also seen during induction (29%) and maintenance (24%) phases [139]. Increased risk for ketamine-related laryngospasm may occur in children with current URI, especially if febrile, if secretions/emesis pool in the posterior pharynx, or if a procedure such as endoscopy stimulates the gag reflex [142, 145, 146].

Recognition of laryngospasm: Early signs of laryngospasm may include coughing. A characteristic stridulous noise can be heard with partial laryngospasm. Chest wall movement is noted but there is a mismatch between the patients' respiratory effort and the small amount of air exchange. If complete laryngospasm occurs, no stridulous noise will be heard and no air exchange or breath sounds will be

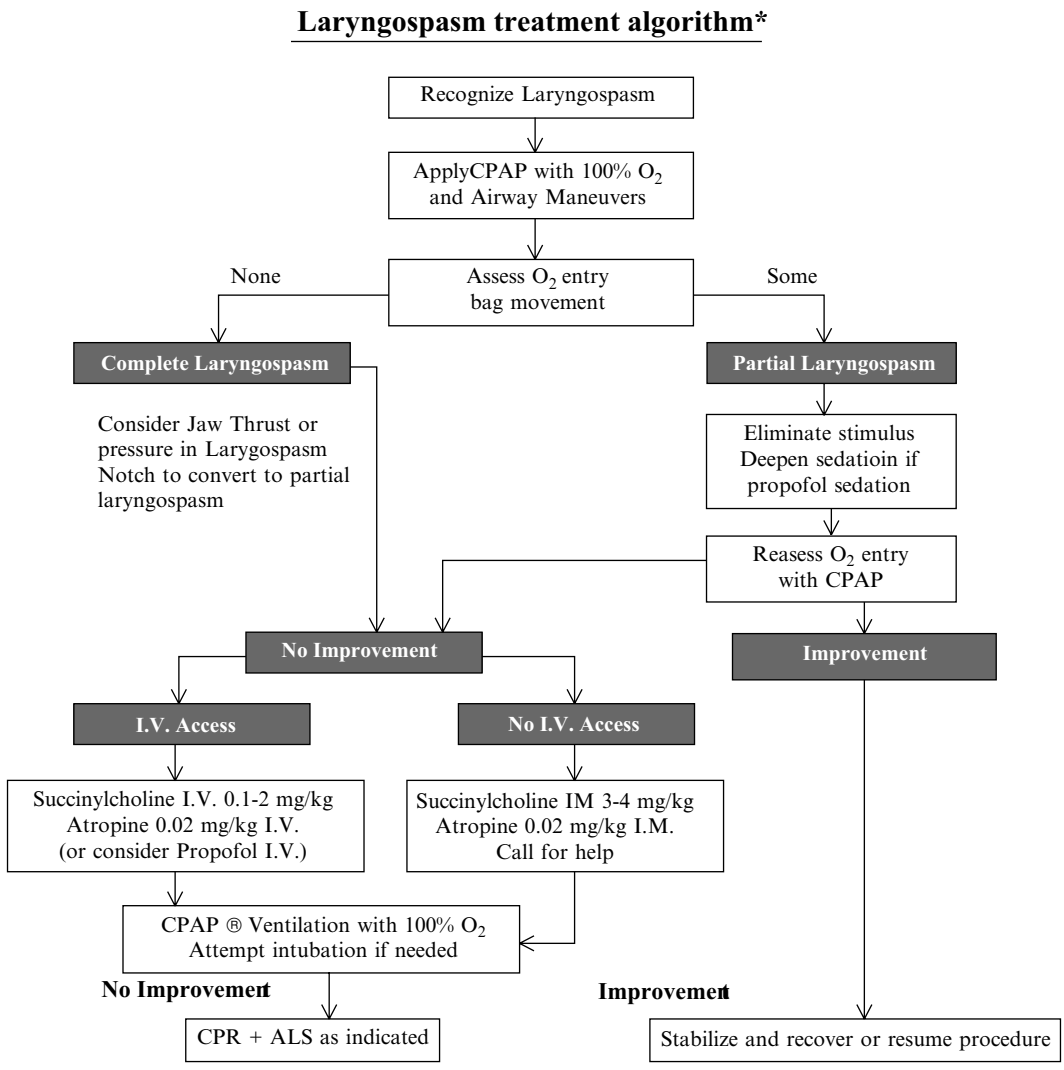

Fig. 15.2 Laryngospasm treatment algorithm (Modified for sedation from Hompson-Evans et al. [361])

noted despite chest wall movement. No ventilation with a bag-mask device will be possible.

Oxygen saturations will drop rapidly if the patient is breathing room air, typically within 30–60 s. If the patient has been preoxygenated, saturations may remain above 90% for 1–5+ min, dropping more rapidly in younger children and infants [112]. Capnographic changes are a very sensitive means of diagnosing laryngospasm. During partial laryngospasm, turbulence affects expiratory flow but the amplitude of the capnogram will correlate with the extent of hypoventilation. During complete laryngospasm the CO_2 waveform will be lost despite chest wall movement [108].

Treatment: (Fig. 15.2) [136] If the patient develops stridor during sedation:

1. *Remove stimulus* to posterior oropharynx; consider gentle suction of excessive secretions, emesis.

2. *Reposition airway* with jaw thrust; vigorous, painful intrusion of the thumbs in the *laryngospasm notch*[2] may help.
3. *Apply CPAP* (continuous positive airway pressure) *with 100% O_2* with anesthesia type bag/mask; CPAP may reduce partial obstruction by distending the posterior pharynx which exerts pull to open the partially closed larynx and vocal cords.
4. *Assess air movement*; if unable to oxygenate with CPAP.
5. Rapidly consider *Atropine 0.02 mg/kg I.V. followed by low-dose succinylcholine* (*0.1–0.25 mg/kg I.V.*) with ventilatory support as needed; [147] consider an additional dose of *propofol* if propofol sedation is underway.
6. If still unable to oxygenate, administer *full-dose succinylcholine* (*1–2 mg/kg I.V. or 3–4 mg/kg I.M.*) followed by intubation.

Attempts to provide intermittent positive-pressure ventilation with a face-mask may distend the stomach and make subsequent ventilation more difficult. In complete laryngospasm CPAP may worsen the obstruction by forcing the area just above the false cords closed. Therefore if complete spasm cannot be broken, early IV agents should be considered [136].

When laryngospasm occurs in the midst of propofol PSA, deepening the sedation with administration of an additional 0.5 mg/kg of propofol has been shown to be an effective treatment for laryngospasm [148]. Transient apnea with this technique should be anticipated.

Low-dose succinylcholine (0.1 mg/kg IV) may be effective in relaxing laryngospasm [147]. Onset of neuromuscular blockade is generally more rapid at the larynx compared with the peripheral muscles [149]. Relaxation of the larynx induced with this small dose will be brief but may allow the patient to be oxygenated by CPAP and intubation avoided. Alternatively, administration of a fully paralyzing dose (1–3 mg/kg IV) followed by intubation should be considered if the patient is rapidly becoming severely hypoxic [136]. The intravenous route is preferred for administration of succinylcholine, but if there is no vascular access, it can be administered intramuscularly at a dose of 3–4 mg/kg. Although full effect may take about 4 min, onset of relaxation of the larynx occurs earlier than maximum suppression of the muscle twitch response and enables ventilation [150].

Succinylcholine administration following hypoxia may be associated with severe bradycardia and even cardiac arrest. *Atropine 0.02 mg/kg I.V.* administered prior to succinylcholine is recommended [151].

Emesis

Nausea and vomiting occur in 5–25% of children during or after ED PSA. Use of opioids before or during sedation increases the likelihood of vomiting [88, 152], whereas concurrent use of midazolam with an opioid [9] ketamine [87], or nitrous oxide [10] reduces the incidence of PSA-related vomiting. Propofol appears to be less emetogenic and may not benefit from addition of midazolam to the regimen. Coadministration of ondansetron (Zofran®) with ketamine reduces vomiting both in the ED and after discharge [92]. Children with a history of prior postoperative nausea and vomiting or with a history of motion sickness are at increased risk for vomiting [153]. Further investigations are needed to better predict sedation associated nausea and vomiting and to determine strategies to significantly reduce this relatively minor but very undesirable adverse effect.

At risk periods: Emesis may occur at any point during procedural sedation, but most commonly is seen during the postprocedure recovery period [9, 10, 88]. Since emesis can occur at any point and with every systemic agent used for procedural sedation, the provider responsible for monitoring the patient's airway should always be vigilant for signs of impending retching and prepared to turn

[2]The laryngospasm notch is behind the lobule of each ear, between the ascending ramus of the mandible and the mastoid process and the base of the skull. Painful pressure at this point over the styloid process is thought to cause afferent input that causes relaxation of the cords by a poorly defined mechanism. This maneuver may also be a modified jaw thrust.

the patient to the side to clear the airway. Suction equipment should be prepared and immediately available during and after all sedations. This equipment is used to finish clearing the emesis from the mouth after the patient stops vomiting. It is also advisable to have a large emesis basin at the bedside during each ED PSA.

Treatment: Emesis During Procedural Sedation

- Position patient's head to side, allow patient to clear own mouth during active vomiting, suction oropharynx with rigid large bore Yankaur type suction tip.
- If using nitrous oxide, immediately remove the mask to allow clearing of emesis and discontinue nitrous use, at least temporarily. It is preferred to allow the patient to hold the facemask during sedation with nitrous oxide so that they can immediately remove the mask if they feel nauseated.

Ondansetron (Zofran®)
An anti-serotonin agent, is not routinely administered to prevent emesis during ED PSA. However, one study of children receiving ketamine for ED PSA, vomiting in the ED or after discharge was less frequent with ondansetron coadministration: (8 vs. 19%), with 9 patients needing to be treated to prevent one episode of vomiting [92]. Ondansetron also may be considered in a child with significant prior history of postoperative nausea and vomiting. Further evaluation of the effectiveness of this antiemetic agent during ED PSA is needed. Other antiemetic agents such as prochlorperazine (Compazine®) or promethazine (Phenergan®) usually are not used because of sedating effects and increased risk for causing dystonic reactions.

Dose: IV, PO: 0.1–0.15 mg/kg, maximum dose 4 mg. Rapidly-dissolving 4 mg oral tabs (ODT) are available and can be split in half for easy administration to young children. Dosing can be simplified by administering ondansetron ODT 2 mg to children 3 years of age and younger and 4 mg to children 4 years of age and older.

Cautions: May rarely cause bronchospasm, tachycardia, headaches, and lightheadedness.

Not requiring patients to drink fluids prior to discharge also may reduce vomiting. Historically, assuring patients can drink prior to discharge has been done to prevent postoperative "dehydration." Given shortened fasting times and the common practice of administration of IV fluids during sedation, the risk of dehydration is low compared to the risk of inducing vomiting [152].

Pulmonary Aspiration

Clinically significant or life-threatening pulmonary aspiration of gastric contents during pediatric procedural sedation is extremely rare. Aspiration occurs in approximately 0.1% of cases under general anesthesia and was noted to have occurred in 4 of 49,836 children undergoing elective propofol sedation/anesthesia but it has not been reported in association with ED PSA [72, 73, 78, 86]. Patients with ASA Physical Status Class III or higher and those requiring intubation are likely at higher risk. Risk for aspiration is likely greater, too, in patients who experience brief periods of apnea or significant respiratory depression as esophageal tone and protective airway reflexes may be absent during these periods and gastric contents may reflux into the trachea with little or no initial patient response. Because of the potential gravity of this adverse event, it is suggested clinicians consider using ketamine or nitrous oxide that better preserve protective airway reflexes or, when possible, lighter sedation combined with local anesthesia for non-fasted emergency patients [154].

Recognition: Clinical symptoms of pulmonary aspiration may include cough, crackles/rales, decreased breath sounds, tachypnea, wheeze, rhonchi, or respiratory distress that were not present before the sedation and present before the end of the ED recovery phase. These are usually accompanied by a decrease in oxygen saturation from baseline, requiring supplemental oxygen, and, if obtained, focal infiltrate, consolidation or atelectasis on chest radiograph [78, 132]. As noted previously, clinically significant pulmonary aspiration may more likely occur in the unresponsive

patient when gastric contents passively flow out of the stomach to the larynx. As the aspiration occurs, there may be little or no immediate signs due to the depth of sedation/anesthesia. The aspiration may become evident as the patient emerges from sedation.

Treatment: If emesis is seen, turn patient to side, allow to retch, and suction posterior pharynx as needed. Administer supplemental oxygen by nasal cannula or mask as needed. Many cases of transient hypoxia will resolve with this simple maneuver. CPAP may improve oxygenation in cases of severe aspiration with alveolar collapse. The majority of children who experience pulmonary aspiration require only close observation and simple supportive care with supplemental oxygen with or without CPAP and recover without sequelae [72, 73, 82, 86]. Endotracheal intubation should be considered if definitive protection of the airway or tracheal suctioning is required; RSI (rapid sequence induction) may be necessary. Uncommonly, severely symptomatic patients may need to be taken to the OR for emergent bronchoscopy with bronchial lavage of particulate matter. Arrange for appropriate continued monitoring, support and work-up as needed including chest radiograph. For symptomatic patients, this usually means inpatient admission to an intensive care unit.

Medications

Basic Pharmacokinetics, Simplified

Parenteral drugs effective for PSA are small, hydrophobic lipophilic compounds that rapidly diffuse out of the bloodstream into the lipophilic tissues of the brain and spinal cord where they cause sedation/anesthesia.

Since the brain receives a disproportionately high percentage of the cardiac output (15–25%) [155], a large portion of a sedative drug injected into the bloodstream circulates on first-pass out of the heart into the brain's circulation and quickly crosses the blood–brain barrier to exert its clinical effects within a single circulation time (first-pass or "one arm-brain" kinetics). As the drug circulates throughout the body and diffuses into muscle, bone, and, at a slower rate, into poorly perfused fat, the blood plasma concentration falls. The concentration gradient between the brain and the blood then favors drug diffusion out of the brain. As the brain's drug concentration falls, the drug effect lessens. This secondary re-equilibration ("bi-phasic redistribution") causes the patient to awaken or respiratory depression to lessen. These effects are relatively independent of metabolic clearance of the drug from the body. PSA drugs' metabolic half-lives tend to be on the order of hours whereas their sedative effect half-lives or "wake-up times" are on the order of minutes [156].

The duration of action of a single intravenous dose is similar for all these anesthetic/hypnotic drugs and is determined by redistribution of the drugs out of the brain. However, after repeated doses or prolonged infusions, a drug's duration of action is determined by complex interactions between the rate of redistribution of the drug, the amount of drug accumulated in fat, and the drug's metabolic clearance. The wake-up time of some drugs such as etomidate, propofol, and ketamine increase only modestly with prolonged infusions while others such as diazepam and thiopental increase dramatically and midazolam less so [156].

A rapidly injected drug travels as a more concentrated bolus on the first-pass out of the heart into the brain circulation than a slowly injected drug that is diluted by the passing blood. Thus, with rapid infusion, the initial concentration gradient between the plasma and the brain is greater. Consequently, the brain's concentration of the drug rises more rapidly and a greater portion of the administered dose enters the brain with resultant deeper sedation than when the same drug dose is slowly infused.

Thus, small doses of medications can have significant clinical effect if administered rapidly. Since the blood–brain concentration gradient also reverses more rapidly with these smaller doses, "wake up" time may be shorter making this strategy beneficial for brief procedures. Importantly, however, clinicians must be aware that rapid changes in the brainstem's concentration of opioid and sedative drugs markedly

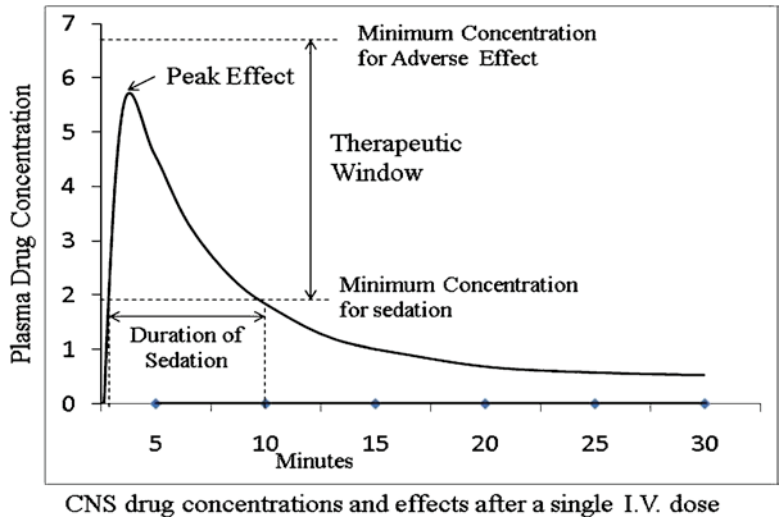

Fig. 15.3 Plasma drug concentration and CNS drug concentrations and effects after a single IV dose

increase the potential for respiratory depression and apnea. As a practical point, this technique can be used only for ketamine administration because it causes markedly less respiratory depression than opioid and GABAergic drugs. This technique needs further study to delineate its safety and effectiveness and is suggested for consideration only by clinicians with extensive experience in ED PSA (Fig. 15.3).

A drug's *Therapeutic Window* is used to describe the difference between the dose of that drug that results in the desired sedative or analgesic effect and the dose that results in adverse effects. A drug with a wide therapeutic window has a greater margin of safety for use for ED PSA. For example, accidental administration of a tenfold greater than intended dose of ketamine will likely result in prolonged recovery but relatively little cardiopulmonary depression [157], whereas the same error with propofol will result in apnea and hypotension [158].

Many reasonable medication options exist for ED PSA [76, 159]. Use of analgesic medication when pain is the primary cause of distress is the key and balancing analgesia with anxiolysis makes sedations more pleasant for patients. For nonpainful procedures when immobility is the primary objective, sedative/hypnotic medications may be chosen. It is recommended that the clinician initially become familiar with a few specific agents or combination of agents that provide the desired effects of analgesia, sedation, and/or anxiolysis. Limiting one's experience to a few agents better enables one to anticipate and manage adverse effects and events associated with those agents. One's pharmacologic armamentarium then can be gradually increased and refined with tailoring of regimens to a specific patient's characteristics. The following section summarizes medication effects and pharmacology in healthy children. Abnormalities in renal and hepatic function can significantly alter these parameters, particularly the duration of effects. In addition, significant variability in effect may occur between individuals due to genetically determined factors such as differences in drug receptor sites, metabolic activation, or clearance. Patients with ASA Physical Status III and higher also have less physiological reserves and therefore are more likely to have adverse effects with smaller doses.

Dosing Details

Titration to Desired Effect

Careful intravenous "titration" of medications using repeatedly administered small doses to achieve the

desired clinical effect enables the practitioner to use the smallest effective dose and reduce the peril of over-sedation with its increasing risks of respiratory depression and aspiration, and, furthermore, hasten recovery [69, 96, 101, 160]. Individual variation in sensitivity to the medication can also be detected, thus a smaller than expected dose may be found adequate for a given individual.

Knowledge of the time to peak effect of the specific medication is necessary to avoid "stacking" of doses when first gaining experience with titration. That is, if, to achieve deeper sedation, a subsequent dose is administered before the peak effect of the preceding dose has occurred, deeper than intended sedation can easily occur. For example, morphine has a peak effect of approximately 10 min. If an additional dose of morphine is administered after 5 min because the patient is still in significant pain, by 15 min after the original dose, when both the first and second doses are near peak effects, the patient may have significant respiratory depression due to an excessive accumulative dose. For this reason, titration is difficult with drugs that have longer than 1–3 min to peak effect time.

When a "typical" total dose for a specific procedure is known, that total dose may be divided and the increments administered at intervals shorter than "the time to peak effect" without likely overshoot. This strategy of repeated administration of fractional doses for fixed dose protocols, e.g., half of the anticipated total dose administered twice with administration separated by a short interval, reduces the risk for significant respiratory depression induced by some agents such as the combined technique using fentanyl and midazolam. This approach is suggested for providers who have less experience with a specific medication.

Intravenous Administration at the Hub

Injecting medications at or near the hub of the indwelling venous catheter allows one to know more precisely when the drug enters circulation and when the entire dose has been administered. This can avoid unintended continued infusion of residual drug in the intravenous tubing when adverse effects are occurring.

Intramuscular Administration

While IM administration avoids the need for placement of an IV catheter, it still requires a feared needlestick and makes titration to effect difficult. More importantly, if a serious adverse event occurs, e.g., severe laryngospasm, an emergent IV for resuscitation medications or fluids may be difficult to place. Specifically, ketamine administered IM has been shown to be effective in achieving sedation. However, the IM route requires either use of a dose large enough to sedate all children, e.g., 4 mg/kg, which will over-sedate some and result in greater frequency of adverse events [137], or painful repeat administration of a smaller dose if the original dose is insufficient. Since the onset of IM ketamine is 5–15 min, titration without over-sedation is difficult. Due to the large dose typically administered IM, recovery is prolonged [161].

Sedative/Hypnotic Agents

Commonly used sedative-hypnotic medications for procedural sedation include the barbiturates, chloral hydrate, propofol, and etomidate. These drugs induce general depression of the central nervous system (CNS) by stimulation of inhibitory gamma-aminobutyric acid (GABA) receptors or other mechanisms which are not yet fully elucidated. None of these drugs have an analgesic effect. While deeply induced sedation, e.g., with propofol, may enable painful procedures to be accomplished, lighter sedation with less respiratory depression may be facilitated by the addition of an analgesic agent as described in subsequent sections. This chapter will review the common sedatives used in the ED with particular focus on their clinical applications and supporting literature from the speciality.

Chloral Hydrate [76]

Indications: Chloral hydrate may be used to provide effective ED PSA in children less than 2 years of age, including those with congenital cardiac anomalies, who are undergoing painless diagnostic studies such as CT and MRI scans. Sedation is achieved

in >80% of young children. Chloral hydrate should not be considered a first line agent in children older than 48 months because of decreased efficacy as compared with younger children. The drug may be administered orally or rectally. The oral preparation has a bitter taste that frequently requires administration in a flavored vehicle to disguise its taste; approximately a third of children may vomit soon after oral administration.

Contraindications/cautions/adverse effects: Children receiving chloral hydrate should be properly monitored and managed by appropriately trained personnel due to the risk of respiratory depression and hypoxia. Chloral hydrate should not be used in children with neurodevelopmental disorders due to an increased incidence of adverse effects and decreased efficacy as compared with healthy children. Chloral hydrate has the potential for resedation and may produce residual effects up to 24 h after administration. The elimination half-life is age dependent with much longer effects in infants. These effects may occur long after the procedure is finished; reports describe infant deaths due to slumping in car seats with obstruction of the airway after discharge. Many infants may have unsteady gait, hyperactivity, or irritability the day after sedation. Other adverse effects include respiratory depression, hypotension, paradoxical excitement (0–15%) vomiting (10–30%), and rarely, hepatic failure, areflexia, jaundice, gastrointestinal hemorrhage, and esophageal stricture [76, 162, 163]. These disadvantages along with its highly variable effects on older children and inherent difficulty with titration of oral medications make this agent less than ideal for children older than 1–2 years of age. Interestingly, children who have been fasted may have increased PSA failure rates. See Mace et al., for further details on dosing and adverse effects [76].

Pregnancy category C

Dose: PO or PR: 50–125 mg/kg; typical initial dose 75 mg/kg. A second dose may be given, if needed, to a maximum of 2 g or 100–125 mg/kg total dose.

Onset/duration: sedation within 30–60 min, recovery by 60–120 min.

Mechanism of action: halogenated hydrocarbon with sedative-hypnotic but no analgesic effects.

Metabolization: rapidly metabolized by hepatic alcohol dehydrogenase to its active compound trichloroethanol and subsequently excreted in the urine [156]. The elimination half-life is age dependent; 40 h in preterm infant, 28 h in term infant, 6–8 h in toddler.

Barbiturates

Barbiturates are pure sedatives with no analgesic effect. They potentiate the effect of gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the CNS, by binding to the $GABA_A$ receptor and prolonging the open time of the membrane chloride ion channel. In addition, barbiturates block the excitatory AMPA receptor [156].

Methohexital (Brevitol®)

Indications: Methohexital administered by either the intravenous, intramuscular, or rectal route can provide effective sedation for children undergoing painless diagnostic studies such as CT or MRI scans. However, because of the readily induced respiratory depression associated with this medication, methohexital has not been used or studied extensively for procedural sedation in children and thus its use should be considered only by experienced and knowledgeable clinicians.

Adverse effects: Respiratory depression and apnea are dose and infusion rate-dependent and are readily induced with intravenous administration but may occur with any route of administration. Hangover-like residual effects may last for 24 h.

Pregnancy category B

Dosages: 1 mg/kg IV; 10 mg/kg I.M.; 25 mg/kg P.R.

Onset/duration: IV: sedation within 30 s, recovery by 20–30 min [164]

PR: sedation within 6–9 min, recovery by 40–60 min [165, 166].

Mechanism of action: ultrashort-acting, highly lipid soluble barbiturate with rapid CNS uptake and redistribution. It has marked sedative-hypnotic but no analgesic effects.

Metabolization: Hepatic degradation with renal excretion results in an elimination half-life of 3.5 h and less accumulation of drug in body tissues compared to other barbiturates.

Pentobarbital (Nebutal®)

Indications: Pentobarbital is a short-acting barbiturate that induces relative immobility and can be safely used to sedate children to facilitate non-painful diagnostic studies such as CT and MRI scans redundant, but supportive measures may include head positioning, supplemental oxygen, and occasional bag-valve-mask ventilatory support [159]. Pentobarbital successfully sedates >97% of children for CT or MRI scans with higher success rates in children younger than 8 years of age [167–169]. Pentobarbital is more effective in providing sedation than midazolam [170] or etomidate [171] and causes fewer adverse respiratory event than propofol [172]. The addition of midazolam with pentobarbital does not appear to increase success rates and prolongs time to discharge [168].

Oral pentobarbital (4 mg/kg) has been found similar to oral chloral hydrate (50 mg/kg) in time to sedation and length of sedation; overall adverse event rate, including oxygen desaturation, was slightly lower with pentobarbital (0.5%) than with chloral hydrate (2.7%) [173, 174]. Of note, a database review found infants younger than 12 months of age sedated for elective CT or MRI with PO pentobarbital (4–8 mg/kg) had comparable effectiveness and fewer respiratory complications compared with IV pentobarbital (2–6 mg/kg); time to sedation was slightly longer with PO than with IV pentobarbital (18 vs. 7 min), but time to discharge (~1 h 45 min) was similar. Total adverse events rate was similar (0.8% [PO] vs. 1.3% [IV]), but oxygen desaturation was slightly more frequent for IV (0.2% [PO] vs. 0.9% [IV]). Sedation effectiveness was comparable (99.5% [PO] vs. 99.7% [IV]), leading the authors to recommend consideration of PO administration for this age group, even when an IV is in place [175]. In a randomized comparison of IV pentobarbital (maximum 5 mg/kg in incremental doses) or oral chloral hydrate (75 mg/kg) prior to MRI, children who received pentobarbital had a higher incidence of paradoxical reaction (14 vs. 9%) and prolonged recovery with a similar failure rate [174].

Adverse effects: Respiratory depression is dose and infusion rate-dependent and is generally less than that seen with equivalently sedating doses of opioids or chloral hydrate [173, 174, 176]. Mild respiratory depression is usually seen at doses required for hypnotic effect. The following adverse events and frequencies have been reported; transient respiratory depression with oxygen desaturation of ≥10% below the baseline in 1–8%, vomiting in ≤1% [168, 177, 178], increased airway secretions, airway obstruction, coughing, and bronchospasm [167–169, 173, 177–179], emergence reactions (hyperactivity in 5–7%) [177, 179] 8.4% in children older than 8 years [179], paradoxical reaction (sustained inconsolability and severe irritability and combativeness for more than 30 min) in 0.01% with oral pentobarbital [173], and in 1.5% with intravenous pentobarbital [168]. Up to 35% of children will have increased sleeping or hangover-like effects in the 24 h following pentobarbital sedation [173, 179]. Pentobarbital should be avoided in children with porphyria.

Pregnancy category D

Dosages: *IV*: Protocol used by author: first dose: 2.5 mg/kg; if needed, subsequent doses: 1.25 mg/kg, may repeat × 3 to maximum of 7.5 mg/kg or 200 mg maximum.

IM: 2–6 mg/kg, to a maximum of 100 mg.

PO or PR (*<4 years*): 3–6 mg/kg, to a maximum of 100 mg.

PO or PR (*>4 years*): 1.5–3 mg/kg, to a maximum of 100 mg.

Onset/duration: The onset of action is related to the route of administration and subsequent absorption. The duration of hypnotic effect is dependent upon redistribution with recovery occurring within 50–75 min after IV or IM administration, even though the biologic half-life in plasma is 15–20 h [176].

After IV administration: sedation by 1–10 min (peak by 5–10 min), recovery by 1–4 h; most patients awakening within 30–60 min [168, 170].

After IM administration: sedation by 10–30 min, recovery by 2–4 h.

After PO administration: sedation by 15–60 min, recovery by 2–4 h.

Mechanism of action: short-acting barbiturate with sedative-hypnotic but no analgesic effects; it induces relative immobility through nonselective depression of the CNS via facilitation of GABA receptors.

Metabolization: hepatic degradation with elimination half-life 15–20 h [176]. This may explain why many parents note it may take their children up to a day to return to normal behavior.

Anxiolytic-Amnestic Sedative Agents

Benzodiazepines

Benzodiazepines produce a range of hypnotic (sedative), anxiolytic, amnestic, anticonvulsant, and muscle relaxant effects via modulation of the $GABA_A$ receptor, the most common inhibitory receptor within the brain. The $GABA_A$ receptor is composed of five subunits each of which has multiple subtypes. The varying combinations of subunit subtypes result in different pharmacological and clinical effects (Table 15.6). When the benzodiazepine binds to its site on the $GABA_A$ receptor, it causes the receptor to have a much higher affinity for the GABA neurotransmitter. This results in the associated chloride ion channel opening more frequently causing the neuronal membrane to become hyperpolarized [156]. Benzodiazepines have no analgesic effect. Benzodiazepines administered without other medications rarely cause severe adverse effects [180]. However, when benzodiazepines are combined with other drugs such as opiates, marked respiratory depression and apnea can readily occur [96]. Midazolam (Versed®) and Diazepam (Valium®) are commonly used benzodiazepines for procedural sedation because of their shorter duration and potent anxiolytic and amnestic effects.

Paradoxical Reactions

Severe behavioral changes, typically during recovery, resulting from benzodiazepines as well as barbiturates have been reported including mania, anger, and impulsivity. Individuals with borderline personality disorder appear to have a greater risk of experiencing severe behavioral or psychiatric disturbances from benzodiazepines. Paradoxical rage reactions from benzodiazepines are thought to be due to partial deterioration from consciousness, generating automatic behaviors, fixation amnesia, and aggressiveness from disinhibition with a possible serotonergic mechanism playing a role [181, 182]. In the context of ED PSA, parents should be forewarned about the possibility of excitability, increased anxiety, and agitation in response to midazolam. Recommendations for management of this adverse effect include protecting patients from self-harm while allowing further recovery, deepening sedation with fentanyl or diphenhydramine or administration of caffeine [181, 183].

Midazolam (Versed®)

Indications: Midazolam is a water soluble benzodiazepine that induces anxiolysis and mild sedation. Most children will not fall asleep with midazolam alone, even at higher doses. Consider another agent or combine with another agent, e.g., pentobarbital, if procedure requires patient to remain motionless (e.g., MRI scan). Midazolam has more potent amnestic effects, quicker onset and shorter duration of action compared to

Table 15.6 Comparison of benzodiazepines

Drug	Dose (mg/kg)	Onset (min)	Peak effect (min)	Duration (h)
Midazolam	0.05–0.15	1–3	3–5	0.5–1
Diazepam	0.1–0.2	1.5–3	1–2	2–6
Lorazepam	0.03–0.05	1–5		3–4

diazepam [184–187]. Since it is water soluble, midazolam can be administered intramuscularly, as well as PO, IV, or intra-nasally (IN). Midazolam may be used for seizure control but longer-lasting agents such as lorazepam are typically used. Midazolam also has antiemetic effects, an additional benefit when coadministered with opioids or ketamine [188].

Contraindications/cautions/adverse effects: Midazolam causes minimal hemodynamic effects (mild hypotension with compensatory tachycardia) but dose and infusion rate-dependent respiratory depression and apnea occur when midazolam is administered in concert with opioids [96]. An important adverse reaction to benzodiazepines in children is the disinhibitory reaction, possibly mediated by central cholinergic mechanisms [181]. Paradoxical excitement or dysphoria during recovery may be increased in older children when midazolam is coadministered with ketamine [87].

Pregnancy category D

Dosages:

IV/IM: Anxiolysis: 0.05 mg/kg IV with maximum of 2 mg; Sedation: 0.1 mg/kg IV with maximum of 5–10 mg. If titrating to effect, administer doses at 3 min or greater intervals to avoid stacking effects. However, the anticipated dose, e.g., 0.1 mg/kg may be divided and administered at 1–2 min intervals to reduce respiratory depression.

PO: 0.2–0.75 mg/kg.

IN: 0.2–0.4 mg/kg (use 5 mg/mL IV solution to reduce volume, use atomizer, or drip slowly): more rapid onset and shorter duration than oral. When administered with an atomizer device, this technique is well tolerated and effective to achieve mild to moderate sedation [189]. If the intravenous solution is dripped into the nares without atomization most children complain of a burning sensation [190–192].

PR: 0.3–0.5 mg/kg, may not be preferred by older children [193, 194].

Onset/duration:

IV: sedation within 1 min, peak effect by 2–6 min, recovery by 30–60 min [195].

IM: sedation within 5–15 min, peaks by 30 min, recovery by 30–60 min [196].

PO: anxiolysis and mild sedation peak within 15–20 min, recovery by 60–90 min [190].

IN: effect within 5–10 min, duration 45–60 min. Use of atomizer results in faster onset.

PR: sedation within 5–10 min, recovery 60 min [193, 194].

Mechanism of action: (see benzodiazepine introduction).

Metabolization: Midazolam is degraded almost completely by cytochrome P450-3A4 in the liver and excreted in the urine. Midazolam metabolites have little CNS activity, unlike those of diazepam.

Pregnancy category D

Reversal: Midazolam-induced apnea or respiratory depression may be counteracted by administration of *flumazenil 0.01–0.04 mg/kg* (*maximum 0.5 mg*) *IV over 30 s* and repeated every 60 s to desired response. A cumulative dose of 3 mg may be necessary. Flumazenil may reverse midazolam-induced hypnotic and amnesic effects but not ventilatory depression [125]. The patient must be closely monitored, typically for 2 h after flumazenil administration, for resedation and respiratory depression. Recurrence of sedation has been reported in up to 7% of cases, most commonly in children under 5 years of age [126]. Flumazenil may cause seizures in patients chronically on benzodiazepine medications and should be used cautiously in patients on medications that can lower seizure threshold.

Diazepam (Valium®)

Indications: Diazepam has excellent antianxiety, skeletal muscle relaxation, and amnestic properties but because its duration of effect is longer than that of midazolam, diazepam is seldom used for ED PSA or preprocedure anxiolysis. It is considered 2–4 times less potent than midazolam.

Contraindications/cautions/adverse effects: Drowsiness may last 2–6 h with resedation occurring at 6–8 h due to enterohepatic recirculation and formation of active metabolites. Like other benzodiazepines, diazepam readily causes respiratory depression with rapid administration.

Diazepam's propylene glycol carrier causes burning sensations on intramuscular and intravenous injection, and erratic absorption with intramuscular administration. Administer with caution in patients with liver and kidney dysfunction.

Dosages: IV: 0.04–0.2 mg/kg/dose q 2–4 h.
PR: 0.5 mg/kg/dose.
PO: 0.12–0.8 mg/kg.

Onset/duration: IV: within 1.5–3 min.
PR: 7–15 min.
PO: 30–60 min.

Mechanism of action: (see benzodiazepine introduction)

Metabolization: Diazepam undergoes hepatic microsomal oxidation with renal excretion. Liver and kidney dysfunction, as well as active metabolites including desmethyldiazepam and oxazepam, may prolong effects.

Pregnancy category D

Other Non-Analgesic Sedative Agents

Propofol (Diprivan®)

Propofol is a sedative hypnotic agent with no analgesic properties [156]. It is the most commonly used parenteral agent for induction and maintenance of general anesthesia in the United States, due in large part to rapid and pleasant recovery from anesthesia induced by this potent agent [156]. Little or no nausea is associated with propofol and it's amnestic effect is similar to that from midazolam [197]. Many adults and older children remark on awakening that they feel as if they have just had a good nap. These characteristics have resulted in propofol's rapid increase in popularity as an agent for scheduled [86, 198] and ED PSA for children [159, 199].

Propofol, however, has a narrow therapeutic window which makes PSA titration to desired effect without over-sedation more difficult than with many other agents. Significant respiratory depression and hypotension are relatively common (see Adverse Effects section) [86, 200]. Propofol can be used alone for painless procedures such as MRI or CT scans, or, at greater doses, for painful procedures. However, because significant respiratory depression or apnea are associated with doses necessary for painful procedures, smaller doses of propofol have been combined with analgesic opiates or ketamine for ED PSA [200–202]. Although combining ketamine with propofol may have theoretical benefit by using lower doses of each agent to reduce the undesirable adverse effects of both agents, a 2007 review of published studies in adults and children found the combination had not demonstrated superior clinical efficacy compared with propofol alone. Studies conflicted regarding reduced hemodynamic and respiratory adverse effects with the combination compared with propofol monotherapy [203]. A comparison of propofol + ketamine to propofol + fentanyl for PSA in toddlers undergoing burn dressing changes found similar minimal impact on blood pressure and respiratory rate but less restlessness with the addition of ketamine [204].

Use of propofol for ED PSA should be preceded by specific training and supervised experience. It is recommended that when propofol is administered, an experienced provider with advanced airway skills be dedicated to administering the sedation and managing the airway and cardiorespiratory status of the patient. In-depth knowledge of adverse effects and advanced airway skills are essential for safe use of this drug.

Pharmacology

The exact mechanism(s) by which propofol exerts global CNS depression has not been fully elucidated. However, there is evidence that propofol potentiates $GABA_A$ receptor activity by slowing the channel-closing time, with lesser effects on $GABA_B$ receptors, modestly inhibits the *N*-methyl-d-aspartate (NMDA) receptor, modulates calcium influx through slow calcium-ion channels, and blocks sodium channels [205].

Pharmacokinetics [158]

Propofol is highly lipophilic and rapidly diffuses from plasma into body tissues, particularly the

highly perfused brain. The onset of action of propofol as determined by time to unconsciousness (i.e., loss of response to voice command) is within 1 arm-brain circulation time (the time required for the drug to travel from the site of injection to the site of action in the brain) and can be as brief as 15–30 s, but is more typically 40–60 s, dependent upon the rate of administration. Since propofol is rapidly distributed from CNS to inactive storage sites such as muscle and fat, recovery from anesthesia is rapid with duration of action about 5–10 min. The short duration of sedation after repeated doses can be explained by rapid metabolic clearance from blood and slow redistribution of the drug from the peripheral tissues. Thus, the pharmacokinetics of propofol after IV administration are best described by a 3-compartment model with rapid distribution of the drug from blood into the brain and other tissues, rapid metabolic clearance from blood, and slow redistribution of the drug from the peripheral compartment back into the bloodstream, resulting in sub-hypnotic plasma levels of drug.

Propofol is rapidly and extensively metabolized in the liver to less active conjugates which are excreted mainly in the urine. Since plasma clearance exceeds hepatic blood flow, it appears that the drug also is metabolized at extrahepatic sites. Mean total body clearance of propofol appears to be proportional to body weight; obese patients have a substantially higher body clearance than leaner individuals.

Indications: Propofol sedation of children in the ED has been reported primarily for fracture reduction with fentanyl, morphine, or ketamine coadministered [200–202, 206]. Sedation or distress scores were low during fracture reduction with propofol + morphine or fentanyl and similar to ketamine + midazolam or morphine + midazolam [201, 202]. Mean recovery times after propofol for these studies were 15–23 min. Unlike other PSA techniques, with the exception of nitrous oxide, repeated or continuous dosing of propofol causes little prolongation of recovery when administered for less than 1–2 h. Thus, after longer procedures such as complex laceration repair or emergent MRI scans during which either repeated doses or continuous infusion of propofol is required, recovery typically is still within 15–30 min [207].

Contraindications/cautions/adverse effects: Transient respiratory depression, apnea, upper airway obstruction, or laryngospasm may occur in many patients, especially during induction of sedation [86, 200, 208]. A recent study suggests that the administration of induction dosages of propofol slowly over 3 min decreases the incidence of respiratory depression [209]. Increasing upper airway narrowing due to muscle relaxation, especially at the level of the epiglottis, has been shown with increasing depth of propofol sedation/anesthesia [210]. Loss of protective airway reflexes during apneic periods may place patients at increased risk of pulmonary aspiration as the ensuing bag-mask positive-pressure ventilation increases gastric pressure and risk of passive regurgitation [86]. Therefore, candidates for propofol sedation must be carefully screened for risks of "full stomachs," URI's, and difficult airways [211]. These events are frequent enough when sedating with propofol that many providers routinely administer supplemental oxygen and monitor with end-tidal capnography, in addition to having a functioning anesthesia or CPAP ventilation bag at the bedside [105, 106, 115].

The main adverse cardiovascular effect of propofol is hypotension, in part related to decreases in peripheral vascular resistance [158, 212]. In spontaneously breathing patients, as much as a 30% decrease in blood pressure may be seen with little or no changes in heart rate [206, 213]. The decrease in blood pressure is dose and infusion rate-dependent and is potentiated by coadministration of opioids such as fentanyl [212, 214]. Propofol may rarely induce profound bradycardia and cardiac arrest in hypovolemic patients or in those at risk for hypotension or with cardiac dysfunction [86, 215]. Administration of additional fluids and a cautious rate of IV infusion may help reduce the risk of propofol-induced hypotension.

Because of the increased risk of apnea and hypotension compared to other agents for PSA, many providers avoid use of propofol in ED patients determined to have difficult airways,

cardiac dysfunction, brief fasting, or ASA Physical Status Classes 3, 4, or 5 [115, 200].

Propofol is formulated as an emulsion in soybean oil, glycerol, and purified egg products because it is essentially insoluble in aqueous solutions. Propofol therefore cannot be administered to patients with allergies to eggs or soy. In addition, to inhibit bacterial growth, some preparations contain sodium metabisulfite which may cause allergic-type reactions in susceptible individuals, including anaphylaxis and life-threatening or less severe asthmatic episodes [158].

Despite the addition of disodium EDTA or sodium metabisulfite to inhibit bacterial growth, significant bacterial contamination of open containers has been associated with serious patient infection. Using aseptic technique, propofol should be administered shortly after removal from sterile packaging [156].

Injection site pain is common with propofol but often may not be recalled due to propofol's amnestic effects. In ED PSA, coadministration of morphine or fentanyl for procedural analgesia may reduce this effect [115]. Lidocaine 0.5 mg/kg administered intravenously immediately prior to propofol infusion and use of large antecubital veins also may help ameliorate this minor adverse effect [158, 201].

Involuntary movement (myoclonus) has been reported in 15–20% of pediatric patients undergoing propofol anesthesia, typically during induction [158]. Myoclonus significant enough to interrupt the procedure, the majority of which were radiological, however, occurred only at a rate of 2/10,000 in elective sedations with propofol [86].

Dosages: Propofol can be administered intravenously in doses of 1–2 mg/kg to achieve sedation. Note however, administration of 2–3.5 mg/kg followed by continuous infusion of 100–300 μg/kg/min is commonly used for induction of general anesthesia [115, 200–202, 206, 216, 217].

Published studies of pediatric ED PSA for fracture reduction used an initial bolus of 1 mg/kg propofol administered over 1–2 min followed by additional doses of 0.5 mg/kg every 1–3 min based on patient response [200, 202, 206]. Mean total propofol doses in these studies were 2.5–4.5 mg/kg. Alternatively, one study followed the initial 1 mg/kg bolus immediately with a propofol infusion at 67–100 mg/kg/min until cast completion; most children required an additional bolus of propofol during the infusion to achieve the desired level of sedation [201]. In each of these studies propofol was administered shortly after morphine or fentanyl administration.

Administration: [158] Commercially available 1% propofol injectable emulsion (10 mg/mL) may be used without dilution. If dilution is necessary, the drug may be diluted with 5% dextrose injection to a concentration of not less than 0.2% (2 mg/mL) in order to maintain the emulsion. Propofol should be discarded if there is evidence of separation of the emulsion. The emulsion should be shaken well just prior to administration.

Using aseptic technique, contents of a vial may be transferred into a sterile, single-use syringe and administered shortly after removal from sterile packaging. The manufacturers state that propofol is compatible with several IV fluids (e.g., 5% dextrose, 5% dextrose and lactated Ringer's, lactated Ringer's, 5% dextrose and 0.2 or 0.45% sodium chloride) when a Y-type administration set is used.

Pregnancy category B

Etomidate

Indications: Etomidate has potent hypnotic (sedative) and amnestic but no analgesic effects. It is in an aqueous solution of propylene glycol therefore, burning on injection is a common complaint. Since etomidate rapidly induces unconsciousness with little hemodynamic effect and clinical recovery occurs within minutes, it is frequently used in the emergency setting to induce unconsciousness prior to neuromuscular blockade during endotracheal intubation [218–220].

Recent reports suggest etomidate may be safe and effective for brief nonpainful procedures such as CT scans and can be combined with fentanyl for fracture reductions. Early reports were inconclusive about the safety and effectiveness of etomidate for ED PSA in children [159, 221–224]. However, a small study of ED pediatric patients

sedated for head and neck CT found successful completion of the CT in 57% with etomidate doses up to 0.3 mg/kg and 76% with doses up to 0.4 mg/kg, in contrast to a success rate of 97% for pentobarbital [171]. Etomidate 0.2 mg/kg IV was infused over 30 s, with additional doses, if needed, of 0.1 mg/kg IV over 30 s at 1 min intervals, to a maximum total dose of 0.4 mg/kg. Duration of sedation was 13 min and parents felt their children returned to normal behavior much earlier than with pentobarbital. A more rapid infusion technique in another study reported a 99% successful completion of CT scans with etomidate in 446 fasted ASA-PS Class I, II children; duration of sedation was 34 min [225]. With a proximal tourniquet in place, 0.5 mg/kg lidocaine (maximum dose 25 mg) was first administered through the intravenous catheter to mitigate burning from the subsequent etomidate infusion, a "mini Bier block" technique. After 1 min, the tourniquet was removed and etomidate 0.3 mg/kg was infused over 2–3 s. If sedation was not adequate, an additional 0.15 mg/kg bolus was administered within 1 min of the initial dose. If needed, an additional 0.15 mg/kg bolus was given during scans requiring multiple views or repositioning. Median total etomidate dose was 3.3 mg/kg. With this technique, 1 patient had apnea and the CT scan was not completed, otherwise significant respiratory depression did not occur. Although most of these children were not ED patients, it suggests this agent may be used successfully for this purpose.

For fracture reduction, etomidate 0.2 mg/kg infused intravenously over 60–90 s resulted in effective sedation in 92% of children compared to 36% with midazolam 0.1 mg/kg IV [226]. Both were combined with fentanyl 1 μg/kg IV. Median recovery time in those reaching adequate sedation was 12 min with etomidate and 24 min with midazolam. Desaturation occurred in 22% of children in both groups; all responded quickly to free flow oxygen administration or head repositioning; no patient experienced apnea or required positive-pressure ventilation. Myoclonus occurred in 22% of patients who received etomidate but it was described as mild and brief and did not interfere with the fracture reduction. Pain on injection of etomidate was noted in 46% of children. Further studies of etomidate are needed to define better safety and efficacy parameters for PSA, particularly in unfasted emergency patients.

Contraindications/cautions/adverse effects: Similar to midazolam, transient apnea with rapid infusion may rarely occur when etomidate is administered alone [225] but respiratory depression may occur in 20% or more of children receiving etomidate coadministered with fentanyl or morphine [226]. Pain with injection in 2–20% and myoclonus in 8–40% of patients are associated with etomidate infusion [222, 227, 228]. When present, myoclonus that can resemble seizures usually lasts less than 1 min and can be decreased by the coadministration redundant of other drugs. These tremors are benign and not epileptiform activity [227, 229].

Although trials investigating etomidate-induced adrenal suppression associated with PSA in noncritically ill children are not available, studies in adults and children have demonstrated cortisol depression for up to 24 h with as little as a single dose of etomidate. This suppression may be clinically significant in patients with hemorrhagic or septic shock leading some to suggest consideration of alternative agents or to combine etomidate with glucocorticoids for induction of unconsciousness for tracheal intubation or PSA in these patients [230–233].

Pregnancy category D

Dosages: 0.2–0.3 mg/kg IV

Onset/duration: onset of sedation within 30–60 s, with duration of deep sedation 3–12 min when using a dose of 0.2–0.3 mg/kg [70]. Sufficient recovery for discharge may take 30–45 min [225].

Mechanism of action: Etomidate, like propofol, is structurally unrelated to other anesthetics. It is an imidazole derivative that is thought to induce sedation through enhanced gamma-amino butyric acid (GABA) neurotransmission [156].

Metabolization: Etomidate is highly protein bound in blood and is degredated by hepatic and plasma esterases to inactive products. It exhibits a bi-exponential decline, with a redistribution

half-life of 2–5 min and an elimination half-life of 68–75 min [156].

Sedative-Analgesic Agents

The following are primary analgesic agents. Sedation generally requires higher doses of opioids or addition of sedative-hypnotic agents, both of which significantly increase respiratory depression. Ketamine induces sedation and amnesia but opioid agents cause little amnesia.

Opiates (Narcotics) (Table 15.7)

Fentanyl (Sublimaze®)

Indications: Fentanyl is a high-potency synthetic opiate with minimal hemodynamic effects. Due to its lipophilic nature and rapid biphasic redistribution, onset of analgesia and sedation occur rapidly with intravenous administration but are of short duration, making it a favorable agent for ED PSA. Fentanyl, by weight, is 80–100 times more potent than morphine. It provides significant analgesia and mild sedation for painful procedures but is not recommended for anxiety control or for control of spontaneous movement. Since fentanyl, unlike morphine, does not cause clinically significant histamine release, it is the opiate of choice in patients who have increased potential for hypotension, e.g., trauma or sepsis [234].

Fentanyl has been administered in oral lozenges (oral transmucosal fentanyl citrate (OTFC)) for ED PSA for laceration repair. However, titration to effect is difficult with this technique and it has been associated with frequent nausea, vomiting (20–50%), and pruritus [235–238]. OTFC has also been used for rapid (30 min) analgesia in children with fractures [239].

Table 15.7 Comparison of opioid medications

Opioid	IV dose (mg/kg)	Peak	Duration
Fentanyl	0.001–0.002 (1–2 μg/kg)	30–60 s	30 min
Morphine	0.1	10 min	4–5 h
Meperidine	1	10 min	2–4 h

Of note, atomized intranasal administration of fentanyl in children in acute pain in the ED has been shown to provide significant pain relief by 5–10 min [240, 241]. One small study of children 1–4 years old undergoing suturing in the ED found intranasal sufentanil, a more potent analog of fentanyl, plus midazolam provided sedation by 20 min without vomiting or other significant adverse events [242]. Further study is needed to clarify safety and efficacy of atomized intranasal techniques for ED PSA.

Fentanyl plus Midazolam: A primary goal with most painful ED PSA is attenuated or blocked unpleasant recall of the procedure. Since fentanyl induces minimal amnesia and cannot completely block procedure-related pain without extreme respiratory depression, it is typically combined with midazolam to induce amnesia for residual procedural pain. Although the combination of fentanyl and midazolam can cause significant respiratory depression [96], both agents have competitive antagonists that readily reverse undesirable effects. If titrated carefully, a small dose of naloxone of 1 μg/kg will reverse respiratory depression but retain much of analgesia effect. This reversibility makes this combined technique an optimum and frequently used approach for ED PSA [159].

The dose of midazolam that maximizes amnestic effect is not well established. Furthermore, while the onset of peak amnestic effect is indistinct, the duration of action appears to be fairly long, hence a broad window within which to administer the analgesic agent, fentanyl. Thus, it is recommended to maximize the capability to administer sufficient amnestic agent by infusing the midazolam before the fentanyl is given since the synergistic respiratory depressant effects of the two medications may limit the ability to administer sufficient amnestic agent if it is given after the fentanyl.

Adequate analgesia for painful procedures always requires sufficient narcotic to cause some degree of respiratory depression (assuming narcotic naive patients). Use of local anesthesia for the procedure, e.g., a hematoma block for fracture reduction, can significantly reduce the amount of systemic analgesic agent needed and thus reduce respiratory depression. It is important

to time the "peak analgesia effect" (peak brain concentration) with "maximal analgesia need" (at time of the maximally painful part of the procedure), hence the analgesic agent is administered after the amnestic agent. The respiratory depression is typically counteracted by the pain of the procedure. Particular attention to ventilatory sufficiency should occur after the painful procedural stimulus ends, since respiratory depressant effects will persist for minutes to hours after the last dose of medication [122]. This adverse effect may be exacerbated by oral or parenteral opioid analgesics administered prior to the PSA.

Contraindications/cautions/adverse effects: Fentanyl, like other opioid analgesics, causes dose and infusion rate-dependent respiratory depression characterized by decreases in respiratory rate, tidal volume, minute ventilation, and ventilatory response to carbon dioxide. Hypotension and bradycardia may also occur with rapid infusion or larger doses. Although return to relative alertness typically occurs within 20–30 min after IV administration, respiratory depressant effects may last several hours. Patients may be awake but need to be reminded to breathe due to the drug's depression of the brainstem response to rising plasma CO_2 [118, 122, 243].

Respiratory depression can be lessened by administering the expected total dose in divided amounts, e.g., 0.5 μg/kg/dose, and infusing each dose over 30–60 s at 1–2 min intervals. Respiratory depression is markedly increased by coadministration of sedative-hypnotic medications such as midazolam or barbiturates [9, 96]. At the level of deep sedation, many children will have respiratory depression or partial upper airway obstruction due to muscle relaxation and may require airway opening maneuvers, supplemental oxygen, or painful stimulation [9].

Respiratory depression is readily reversed by the competitive antagonist naloxone. Titration of naloxone in small doses of 1 μg/kg stopping at the endpoint of reversal of respiratory depression will retain much of the analgesia effect. Repeated doses may be necessary as respiratory effects may outlast the reversal effects of naloxone. Administration of a "full" dose of naloxone may cause significant pain, hypertension, tachycardia, vomiting, and other undesirable adverse effects.

Chest wall rigidity may occur with rapid infusion of large doses (usually >5 μg/kg), especially in infants. This life-threatening adverse effect will manifest by lack of spontaneous chest wall movement, dropping oxygen saturations, and an inability to ventilate the patient with positive pressure by bag and mask. Reversal with naloxone or paralysis with succinylcholine may be needed to manage this adverse event.

Pregnancy category C

Dosages: *For analgesia*: 1–2 μg/kg, intravenously. Titrate to effect by administering doses of 0.5 μg/kg over 15–30 s, repeated every 1–2 min. A total dose of 1–2 μg/kg usually can be administered without causing significant respiratory depression, unless coadministered with midazolam. For significantly painful injuries, an initial dose of 1 μg/kg usually may be administered safely over 30 s.

For ED PSA: *Fentanyl + Midazolam*: Midazolam, 0.05–0.1 mg/kg intravenously over 1–2 min is administered first, titrated to an endpoint of drooping eyelids, slurred speech. A total dose of 10 mg likely is sufficient for amnesia in large adolescents. Then Fentanyl, 0.5 μg/kg intravenously over 30 s, repeat to an endpoint of decreased patient responsiveness to a relevant painful stimulus such as squeezing the fracture site or palpating the abscess. If local anesthesia is used for the procedure, approximately 1 μg/kg fentanyl may be sufficient. For intensely painful procedures, such as fracture reduction without a hematoma block, up to 2 μg/kg may be necessary [9]. Respiratory depression is likely at this dose therefore, time the end titration of fentanyl as the painful part of the procedure is begun; the procedure-related pain will stimulate the patient and counteract some of the respiratory depression. Additional doses of fentanyl may be administered after about 10 min if the patient becomes agitated or manifests significant pain during longer procedures.

Fentanyl comes in 2 mL vials of 50 μg/mL. Titration is easier and safer if the concentrated fentanyl is diluted to 10 μg/mL by adding 2 mL of fentanyl to 8 mL of normal saline, resulting in 10 mL of 10 μg/mL.

Onset/duration: Analgesia with mild sedation after IV administration of fentanyl is within 30–60 s with greatest sedative-analgesic effects lasting 5–10 min. Although return to relative alertness typically occurs within 20–30 min after IV administration, respiratory depressant effects may last several hours. Patients may be awake but "forget to breathe" due to the drug's depression of the brainstem response to rising plasma CO_2 [118, 122, 243].

Mechanism of action: Fentanyl is a high-potency mu agonist opiate 50–100 times more potent than morphine [234].

Metabolization: Fentanyl is metabolized in the liver and excreted in the urine. There are no active metabolites [234].

Morphine

Indications: While the "standard" for analgesia, morphine is typically not used for procedural sedation because its slow onset of peak analgesic effect (~10 min) makes titration difficult. Repeating a dose before 10 min leads to "stacking," i.e., administering a second dose before the peak effect of the first dose results in unnecessary excess medication administration, overshooting the intended level of analgesia, and is associated with excess adverse effects such as respiratory depression. Morphine is commonly administered to provide baseline analgesia if the patient is in pain from an injury, abscess, etc. Additional analgesia, typically with a different agent such as fentanyl or ketamine, is then administered for the procedure.

Contraindications/cautions/adverse effects: Additional administration of a benzodiazepine for anxiolysis increases the respiratory depression associated with morphine administration. Morphine induces histamine release and may result in hypotension, nausea/vomiting, dizziness, pruritus; histamine release may exacerbate asthma. Pruritus can be treated with diphenhydramine.

Dosages: IV: 0.05–0.1 mg/kg, titrated to the effect of pain relief. Opioid naïve patients may experience less nausea if the expected dose is divided. For example, an 80 kg teenager will likely better tolerate two 4 mg doses administered 10–15 min apart.

Onset/duration: 1–3 min, peak 10–20 min; duration of significant analgesia 1–2 h

Mechanism of action: mu agonist (analgesia), weak kappa agonist (respiratory depression).

Metabolization: glucuronidated in the liver and excreted in the urine: 10% metabolized to active metabolite which can accumulate in children with renal failure.

Pregnancy category C

Meperidine (Demerol®)

Indications: Although a potent opioid, meperidine, like morphine, is seldom used for procedural sedation because its long time to peak effect (~10 min) makes it difficult to titrate without overshooting (stacking) the intended level of analgesia and sedation. In addition, meperidine causes histamine release at a greater frequency than do other opioids and its atropine-like effects may cause tachycardia and euphoria.

Contraindications/cautions/adverse effects: Interaction with MAO inhibitors may be catastrophic resulting in hypertension, excitation, tachycardia, seizure, and hyperpyrexia. Biodegradation to the active metabolite normeperidine (elimination half-life of 15–40 h) results in prolongation of effects. With large or repeated doses, accumulation of normeperidine may cause nervous system excitation with tremors, muscle twitches, and seizures.

Dosages: IV/IM: 1 mg/kg.

Onset/duration: IV: 1–5 min, peak by 10 min; duration of 1–2 h.

IM: peak effect by 10 min, duration 1–2 h.

Mechanism of action: a phenylpiperidine opioid with potent analgesic effects.

Metabolization: hepatic degradation forms active metabolite normeperidine (elimination half-life of 15–40 h) which results in prolongation of effects and has adverse effects as noted earlier.

Pregnancy category C

Codeine

Codeine is well absorbed after oral administration but the drug must be metabolized by the liver to morphine to have an analgesic effect. Since up to 35% or more of people are slow or non-metabolizers, codeine is an ineffective analgesic

agent for many [244, 245]. Conversely, ultrarapid metabolizers may experience reduced analgesic effect but increased adverse effects from relatively small doses [246]. For these reasons, oxycodone is the oral analgesic of choice in the author's ED.

Oxycodone

Indications: Oxycodone, an opioid analgesic medication originally synthesized from opium-derived compounds, is readily absorbed by the oral route and is often administered for painful conditions when no IV access is established, e.g., at triage for possible fractures or burns [247]. It can also be used to augment sedation for painful procedures, e.g., with nitrous oxide for abscess I&D or fracture reduction [88]. Oxycodone is preferred because, unlike codeine, it does not require metabolism to an active form. Oxycodone may cause less nausea than codeine [2] but one comparison found no difference in vomiting or other adverse effects at analgesically similar doses [247].

Contraindications/cautions/adverse effects: Oxycodone, as do other opiates, significantly increases frequency of vomiting when combined with other analgesic regimens, e.g., with ketamine or nitrous oxide. Vomiting prior to ED discharge after PSA increased from approximately 10% with ketamine + midazolam [9] or nitrous oxide [10] to 25% when oxycodone had been administered in triage [88]. Oxycodone also causes dose-dependent respiratory depression by blunting the brainstem response to increasing levels of carbon dioxide. A dose of 0.2 mg/kg administered to children with painful injuries caused tiredness but no clinically apparent changes in ventilation or oxygenation [247]. At a dose of 0.3 mg/kg administered to young children in preparation for painful abscess I&D, we have observed many patients become sleepy but are easily aroused with verbal stimuli and oxygen saturations usually remain within normal ranges as they breathe room air; however, these children should routinely be monitored for respiratory depression after this larger dose.

Dosages: 0.05–0.15 mg/kg for out of hospital analgesia. *For procedural analgesia, 0.2–0.3 mg/kg,* with the larger end of the range for younger children for fracture reduction, burn debridement, or abscess management. Since absorption after gastric administration has large interindividual variation in the rate and extent of absorption [248], the higher dose is not recommended for home use due to the potential for oversedation. Similarly, oxycodone should be used with caution in infants younger than 6 months of age due to marked variation in clearance [249].

Onset/duration: Analgesia begins within 30 min, peaks at ~1 h; duration 2–3 h.

Mechanism of action: mu agonist (analgesia), weak kappa agonist (respiratory depression).

Metabolization: Oxycodone is metabolized by the cytochrome P450 enzyme system in the liver with up to 20% excreted unchanged in the urine. Thus, patients with poor renal function may accumulate higher plasma levels.

Pregnancy category B (D for prolonged use).

NMDA (*N*-Methyl-D-Aspartate) Antagonists

Ketamine (Ketalar®)

Ketamine is a phencyclidine derived lipophilic dissociative agent with rapid biphasic redistribution. Potent analgesic and amnestic effects with relative lack of cardiopulmonary depression make ketamine quite likely the most widely used and appropriate agent for ED PSA [159, 250]. The American College of Emergency Physicians (ACEP) has recently published a Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation: 2011 Update [251]. The major changes in these guidelines as compared to the former of 2004, are summarized in the Fig. 15.4 [79, 251]. During fracture reduction, children receiving ketamine demonstrated significantly less distress and less respiratory depression than those receiving fentanyl or propofol coadministered with midazolam [9, 202]. Ketamine also induces significant amnesia and effective PSA for other intensely painful ED procedures such as burn debridement and abscess incision and drainage and relative immobility for procedures during which occasional spontaneous

General
- Expansion of guideline to include adults

No Longer Contraindications
- Administration for ages 3 to 12 months
- Minor oropharyngeal procedures
- Head trauma

Route of Administration
- Emphasis on IV over IM route when feasible

Coadministered Medications
- Routine prophylactic anticholinergics no longer recommended
- Routine prophylactic benzodiazepines may benefit adults but not children
- Prophylactic ondansetron can slightly reduce vomiting

Fig. 15.4 Major changes in the 2011 guideline (reproduced from Green et al. [251], with permission from Elsevier)

movement is tolerated, such as complex laceration repair and brief radiological procedures such as CT scans or joint aspiration [79, 159].

Ketamine has unique and diverse mechanisms of action with beneficial and potentially adverse effects. Ketamine interacts with multiple binding sites including *N*-methyl-d-aspartate (NMDA) and non-NMDA glutamate receptors, nicotinic and muscarinic cholinergic and opioid receptors, and less so, peripheral neuronal sodium channels [252]. Ketamine's primary site of anesthetic action is in the CNS in thalamocortical pathways and the limbic system where it binds to a site on postsynaptic NMDA channels which regulate transmembrane calcium, sodium, and potassium flux. This binding inhibits glutamate activation of the channel in a noncompetitive manner and is time and concentration dependent [119, 252, 253].

Circulatory Effects

In contrast to other sedative and analgesic agents, cardiac output, including heart rate and blood pressure, is usually well maintained with ketamine administration, even at deeper levels of sedation or anesthesia. Ketamine causes 10–30% increases in blood pressure and heart rate by blocking reuptake of catecholaminergic hormones norepinephrine, epinephrine, dopamine, and serotonin. These effects may increase intracranial pressure and caution has been suggested with its use in patients with known intracranial pathology causing increased intracranial pressure. However, use of ketamine in ventilated patients with head trauma has been shown safe and not to impact intracranial pressure differently from opioids [254, 255]. Use of ketamine in the ED for rapid sequence intubation of patients with head trauma has also been advocated as safe [256]. Of note, ketamine also has a direct negative inotropic effect on the heart that is usually clinically inapparent due to the sympathetic stimulation [257]. In critically ill patients whose catecholamines are depleted due to maximal compensation for hypovolemia, hypoxemia, fluid-electrolyte, acid-base, and other physiologic insults, administration of ketamine may cause marked hypotension and bradycardia [258].

Ventilatory Effects

In marked contradistinction to other sedative-analgesic agents, doses of ketamine typically used for ED PSA rarely cause depression of pulmonary gas exchange or relaxation of upper airway muscles [259]. Intravenous infusion of 2 mg/kg of ketamine over 1 min characteristically causes no significant effect on respiratory rate, tidal volume, minute ventilation, or end-tidal CO_2, thus maintaining adequate gas exchange during unobstructed spontaneous room air breathing [260]. Furthermore, ketamine does not significantly decrease thoracic or airway muscle activity [259, 261, 262], or impair lung ventilation distribution, functional residual capacity, or minute ventilation with intravenous doses of 2 or 4 mg/kg [134]. These effects and maintenance of positive end-expiratory pressure (PEEP) [263] result in lack of peripheral alveolar collapse and regional hypoventilation seen with propofol and opioid agents. Interestingly, relatively low-dose ketamine (1 mg/kg administered intravenously over 5 min, i.e., 0.2 mg/kg/min) to adults caused respiratory stimulant effects with three distinct phases: increased tidal volumes (deep breathing) was followed by increased respiratory rates and then large tidal volumes with low respiratory rates and occasional brief apnea, possibly compensating for hypocarbia due to the preceding hyperventilation [264]. These findings are consistent with the mild increase in respiratory rate

with maintenance of normal oxygen saturation and end-tidal CO_2 noted in children receiving intravenous ketamine 1.5 mg/kg over 1 min for ED PSA [111].

Reduced responsiveness to increased CO_2 and hypoxemia, however, have been demonstrated during the initial period after a bolus of ketamine when plasma levels are high and resolving as levels decrease [260, 265, 266]. This suggests the possibility of apnea in sensitive individuals or a delayed response to hypercarbia if airway obstruction occurs during induction of sedation and may explain the case reports of brief respiratory arrest after administration of intramuscular ketamine for ED PSA [120, 267, 268]. A case series of 18 children who inadvertently received 5–100-fold larger than intended doses of ketamine described respiratory depression and prolonged recovery but no residual effects except for one critically ill infant who died [157]. A meta-analysis of more than 8,000 children who received ketamine for ED PSA found that the overall incidence of airway and respiratory adverse events (upper airway obstruction, apnea, oxygen desaturation ≤90%, or laryngospasm) was 4%. Increased risk was found in younger children and teenagers, those receiving more than 2.5 mg/kg initial or 5 mg/kg total doses, and those receiving coadministered anticholinergic or benzodiazepine medications [137]. Airway and respiratory adverse events occurred at twice the overall rate in children younger than 2 years, except for laryngospasm or apnea which were not increased. The overall frequency of airway and respiratory adverse events in adolescents 13 years or older was almost 3 times greater with more apnea but less laryngospasm. The overall frequency of apnea was 0.8% in this series. Coadministration of other sedative-analgesic agents such as midazolam or morphine and young age also have been found by others to be associated with greater respiratory depression [87, 269].

Protective Airway Reflexes

Preservation of upper airway protective reflexes, even at deeper levels of sedation or anesthesia, reduces the risk of pulmonary aspiration and thus makes ketamine one of the safest agents for ED PSA in unfasted children, yet, paradoxically, it may increase the risk for one of the most significant life-threatening sedation related adverse events, laryngospasm [134–136]. The incidence of laryngospasm in ketamine-based pediatric ED PSA is difficult to determine as it is a rare event and large sedation databases are not available for estimation. The meta-analysis of pediatric ketamine-based ED PSA found an incidence of laryngospasm of 0.3%; the only identifiable association with greater risk was an initial intravenous dose of greater than 2.5 mg/kg but data was unable to be analyzed for URI, wheezing, or other risk factors noted with general anesthesia. Young age and oropharyngeal procedures (excluding endoscopy) were not associated with increased risk [137]. Although in the past, the prophylactic administration of anticholinergics were believed to reduce the incidence of secretions, laryngospasm, and respiratory complication, this is no longer held true. Rather, a recent matched case-control analysis of 8,282 ketamine procedures in the emergency department revealed no association between age, dose, procedure, medical status, route of delivery, and the administration of anticholinergics with the occurrence of laryngospasm [270]. This data is important because it identifies the occurrence of laryngospasm as an unpredictable and idiosyncratic reaction. All practitioners, thus, who administer ketamine should be prepared to identify and treat laryngospasm.

Initial management of laryngospasm should include airway opening maneuvers (straightening, jaw thrust) and administration of supplemental oxygen, preferably by continuous positive airway pressure (CPAP). If these are insufficient to maintain oxygenation, low-dose succinylcholine should be considered (~0.1–0.2 mg/kg IV); if this low dose does not improve oxygenation, a full paralytic dose of 1–3 mg/kg succinylcholine should be administered. Laryngospasm induced by ketamine may be brief or it may be recurrent and it may occur during emergence as well as induction or mid-procedure [133]. Please see section on "Management of Laryngospasm."

Sedative-Analgesic Effects

Sedation and dissociation induced by ketamine likely occur primarily from blockade of the excitatory effects of glutamate, the most prevalent CNS

excitatory neurotransmitter. By binding to the neuronal membrane's *N*-methyl-d-aspartate (NMDA) glutamate receptor complex associated with transmembrane calcium channels, ketamine prevents or reduces neurotransmission of pain and other stimuli by interfering with the calcium influx necessary for electrical propagation [252].

Dissociative Effects

Ketamine is classified as a dissociative general anesthetic agent because EEG and fMRI recordings demonstrate electrical activity of the thalamus that is no longer synchronized with or is "dissociated" from the limbic system after ketamine administration [271]. The thalamus is believed to process and relay sensory information selectively to specific areas of the cerebral cortex and plays a major role in regulating arousal, the level of awareness, and activity as well as processing auditory, somatic, visceral, and visual sensory input [135]. It is thought this dissociative effect is the primary mechanism for preventing patients' response to pain or other sensory stimuli after ketamine administration. More precise understandings of the mechanisms are under investigation. The patient who has received ketamine without an adjunctive sedative agent may have his eyes open but be unresponsive to the environment, described by some as if "the lights are on but nobody's home." This catatonic stare may be frightening to unprepared observers such as family members.

Prolonged Analgesic Effects

A relatively unexplored potential analgesic benefit of ketamine use for ED PSA is reduction of wind-up and central sensitization [272]. Brief noxious stimulation of peripheral tissue receptors initiates rapid neural transmission along myelinated and unmyelinated axons to the nerve's central terminus located within the dorsal horn of the spinal cord and induces release of excitatory neurotransmitters, primarily glutamate, into the dorsal horn synapse. The glutamate initiates rapid firing of postsynaptic AMPA and kainate receptors, resulting in sharp "first" pain and reflex withdrawal from the stimulus, soon followed by dull, aching, burning, and poorly localized "second" pain. Persistent noxious stimulation of these peripheral nerves induces pre- and postsynaptic neurons in the dorsal horn to undergo changes in function, chemical profile and structure that result in propagation of neural impulses at lower than normal thresholds, prolonged discharge, and widening of receptive fields. These changes have been termed "wind-up" and "central sensitization" hyperalgesia wherein successive similar stimuli cause increasing pain or normally subthreshold stimuli, such as light touch, produce intense pain at and adjacent to the site of original injury. Wind-up and central sensitization occur primarily by greater and more prolonged opening of postsynaptic NMDA channels to allow Ca^{2+} influx which reduces transmembrane potential and facilitates postsynaptic depolarization [273]. This central facilitation manifests within seconds of a nociceptive stimulus and can outlast the stimulus for hours, days, or longer if the stimulus is maintained, even at low levels [274, 275]. Experimental and clinical studies in adults have demonstrated that a single small dose of ketamine reduces the magnitude of hyperalgesia and windup-like pain [276–279]. Adults undergoing elective orthopedic or abdominal operations, for example, had reduced postoperative pain and marked reduction of opiate medication use for hours to days when as little as 50 mg of ketamine was added to their general anesthetic regimen [135, 280, 281]. Continued low-dose infusion of ketamine has also been shown to markedly augment morphine for analgesia after musculoskeletal injury in adults [282].

Paradoxically, opiates have been found to induce short-lasting analgesia and long-lasting hyperalgesia [283]. This opiate-induced hyperalgesia is also under the influence of excitatory neurotransmission and is similarly reduced by ketamine blockade of the NMDA-glutamate receptor [284–286]. Whether these prolonged beneficial effects occur with ketamine administration for ED PSA after an acute traumatic injury has yet to be explored.

Neurotoxicity

Concern has been raised about use of ketamine in children due to evidence of neurotoxicity in animals after high doses. Toxicity manifested as neuronal vacuolization has been found

within specific areas of the midbrain of rats after administration of 40 mg/kg ketamine, but not after doses of 5, 10, or 20 mg/kg [287]. Other investigators found no evidence of neuronal injury (apoptosis) in 7 day old rat pups after single doses of 25, 50, or 75 mg/kg; only with repeated injections of ketamine 25 mg/kg every 90 min for 9 h was any evidence of toxicity noted [288]. Of possible pediatric relevance, neuronal vacuolization was not found even with large doses of a potent ketamine-like drug (MK-801) in animals prior to puberty [289]. In addition, GABAergic drugs (e.g., diazepam) and alpha$_2$ agonists (e.g., clonidine) markedly reduce the excitotoxic effects of ketamine-like drugs; it has been suggested these should be coadministered with ketamine as a neuroprotective strategy [290].

A marked increase in normal CNS apoptosis or programmed cell death and some evidence of subsequent learning disabilities in association with administration of ketamine, ethanol, benzodiazepines, propofol, and volatile anesthetics also has been found in rodent animal models [291–293]. Of potential importance, the brain area most affected may vary by species. In rodents, key regions for learning are targeted whereas in the monkey, perhaps less essential cortical redundant cells are more affected [294]. While it is difficult to compare the effect of specific dosages across species, doses that achieve similar clinical effects as PSA have been shown to increase CNS apoptosis in infant mice [295]. Although ketamine has been used extensively in children without apparent ill effect, these studies raise serious concerns that are the targets of ongoing investigations.

Psychotomimetic Effects

Transient ketamine-induced schizophrenia-like symptoms including hallucinations, delusions, illogical thinking, poverty of speech and thought, agitation, disturbances of emotion and affect, withdrawal, decreased motivation, decreases in memory, and dissociation are well described in adults and a major constraint to use of the drug [296–299]. These symptoms occur when plasma levels of ketamine are relatively low and thus are seen during recovery from sedation. Similar to onset of schizophrenia, these symptoms are thought to be more common in adults and adolescents than in prepubertal children, but this has not been confirmed in children or in association with ED PSA [87, 253, 257, 300–302]. Dependent upon definitions, overall emergence phenomena are well tolerated and occur in approximately 5–25% of children recovering from ED PSA with ketamine, as well as with other drug regimens, and in similar frequency at home within days of discharge [9, 87, 301, 303]. However, significantly unpleasant and disturbing phenomena (i.e., nightmares, hallucinations, and severe agitation) occur unpredictably in approximately 5% or fewer children and are also seen with other drug regimens such as fentanyl plus midazolam [9, 87]. Midazolam routinely administered after ketamine or mixed within the same syringe does not appear to reduce significant recovery dysphoria and may increase agitation in postpubertal children [87, 304]. Of interest, preinduction anxiety and agitation have been correlated with emergence delirium for both ED PSA and general anesthesia [304, 305]. Whether pre-sedation midazolam for anxiolysis may reduce recovery dysphoria in significantly anxious children undergoing ED PSA, as has been shown with general anesthesia, is unclear [303, 306].

A potentially effective strategy to reduce emergence delirium, and one regularly employed by the author and others, is to inform the patient to expect transient funny dreams, diplopia, blindness, etc., and to have pleasant thoughts during induction of sedation [307].

Other Adverse Effects

Ketamine administration occasionally causes an evanescent erythematous rash shortly after infusion, and more commonly, double vision and dizziness during emergence from sedation, hypersalivation, typically with repeated or larger doses, and vomiting [9]. Vomiting in children who receive ketamine without adjunctive medications for ED PSA has been reported in 10–20% of children [87, 92]. Fortunately, vomiting almost always occurs during the recovery period and after discharge from the ED [9, 308].

Coadministration of opioids such as morphine or oxycodone increases emesis whereas coadministration of midazolam with ketamine significantly reduces the likelihood of vomiting (19 vs. 10%) [87] as does ondansetron (13 vs. 5%) [92]. Since vomiting may be more likely to occur in older children, ondansetron should be especially considered in children older than 5 years [92]. Vomiting does not appear to be linked to the length of pre-sedation fasting or the dose of ketamine administered [63, 90, 309].

Ketamine associated hypersalivation is thought to be mediated via cholinergic effects [135]. Because of concern that excess saliva may trigger laryngospasm and other adverse airway events, anticholinergic antisialagogues such as atropine or glycopyrrolate have traditionally been coadministered with ketamine [119, 253]. However, an unblinded observational study of approximately 1,000 children receiving intravenous ketamine without an antisialagogue for ED PSA, mean dose 2 mg/kg, found no significant hypersalivation or adverse airway effects [144]. In contrast, a randomized blinded trial of intramuscular ketamine, 4 mg/kg, with or without atropine, found increased salivation but no adverse airway events in those receiving ketamine [143]. These studies suggest hypersalivation may be dose related. Importantly, a meta-analysis found an increased occurrence of respiratory adverse events associated with antisialagogues [137]. Because of these studies and that "dry mouth" is a common complaint after atropine or glycopyrrolate, the author no longer routinely administers an antisialagogue when a single intravenous ketamine dose or total doses of 2 mg/kg or less are used for ED PSA.

Contraindications/cautions/adverse effects: (please see specific effects).

While much less common than with other ED PSA regimens, respiratory depression, apnea, and upper airway obstruction may occur with ketamine administration [268]. When identified by close monitoring and direct observation, these adverse effects are usually easily managed with simple maneuvers such as jaw thrust and airway straightening [308]. Ketamine preserves cardiac output in healthy patients but should be used with caution in patients manifesting shock as it may cause cardiac depression and profound hypotension [258].

Psychotomimetic effects, e.g., hallucinations, paranoia, and other schizophrenia-like symptoms, occur unpredictably and usually become manifested as dysphoria during recovery. Some believe these symptoms may occur more frequently in postpubertal children and in children with psychiatric disorders. Since the pathologic mechanisms of schizophrenia appear to be similar to ketamine induced effects, it is recommended to avoid use of ketamine in patients with psychiatric disorders and those whose close relatives carry these disorders. Although not well studied, children with attention deficit and hyperactivity disorders (ADHD) do not appear to have increased susceptibility to psychotomimetic effects. Ketamine is used routinely with and without midazolam in the author's ED for intensely painful procedures in adolescents; all verbal children are informed prior to sedation of what they might experience during recovery and given the suggestion to think of pleasant circumstances as sedation is induced. Midazolam routinely administered after ketamine or mixed within the same syringe does not appear to reduce dysphoria during recovery from ketamine sedation and may increase dysphoria in teenagers [87, 304]. Highly anxious children may benefit from receiving anxiolytic doses of midazolam well before ketamine, as has been shown with general anesthesia [306, 310, 311].

Ketamine is available in concentrations of 10, 50, or 100 mg/mL. For intravenous sedation, it is recommended only the 10 mg/mL concentration be used in order to reduce the risk of overdose and to facilitate titration to desired effect. It is also recommended that only one concentration be routinely available in the ED to reduce the likelihood that a more concentrated solution and thus, larger dose than intended, be inadvertently administered.

Pharmacokinetics

In unpremedicated children and adults, approximate ketamine distribution half-life is 24 s, redistribution half-life 4.7 min, and elimination half-life 2.2 h [312, 313]. The redistribution

half-life of 5 min is consistent with the typical deepest sedation period of 5–10 min observed with single dose ketamine for ED PSA. Midazolam or diazepam coadministration with ketamine may delay hepatic metabolism, yet it does not seem to prolong recovery although the midazolam sedative effects may prolong discharge [87, 314].

To reliably achieve the dissociated state for ED PSA, a minimum dose of ketamine 1.5–2 mg/kg administered intravenously over 30–60 s or 4–5 mg/kg administered intramuscularly are generally recommended [79, 251]. However, studies have found smaller intravenous or intramuscular doses to be effective, particularly when coadministered with midazolam [9, 88, 161, 315, 316]. Recent pharmacokinetic studies of ketamine ED PSA in children have helped elucidate why these different dosing strategies can be effective.

Age-specific ketamine pharmacokinetic profiles based upon measurement of plasma concentrations of ketamine in children 1.5–14 years of age who were undergoing ketamine ED PSA have been determined [317]. These profiles were then used to simulate several dosing strategies and recovery periods designed to achieve 15 min of very deep sedation/anesthesia (unresponsive or arouses, but not to consciousness, with painful stimulus) [160]. They predict, a typical 6-year-old child would recover (drowsy, eyes open or closed but easily arouses to consciousness with verbal stimulus) by 70 min after a 2 mg/kg infusion over 30–60 s. An alternative strategy of an initial bolus of 1.25 mg/kg with a subsequent half dose (0.625 mg/kg) "top-up" at 8 min would achieve recovery by 30 min. Finally, an initial dose of 0.3 mg/kg followed by an infusion of 3 mg/kg/h for 15 min would result in recovery by 20 min after the infusion was stopped. These and doses for other ages are listed in Table 15.8.

As with most drugs, between-subject variability has been found in ketamine effect and clearance. The mean target ketamine plasma concentration of 0.65 mg/L would only be effective in 50% of children; a concentration of 1.59 mg/L would be required to achieve a similar effect, with longer recovery, in 95% of children [160]. The rate of plasma clearance in children is similar to that in adults and correlates with hepatic blood flow. Clearance increases in a nonlinear function with decreasing age and is reflected by higher dose requirements (mg/kg) to maintain the desired effect in younger children. Size accounts for only about half of the clearance variability; it is unknown what impact pharmacogenomics add. In an individual child, titration to the desired depth of sedation must be gauged clinically.

Table 15.8 Ketamine dosing schedules to maintain very deep sedation levels for 15 min [160]

Age	Single dose (recovery ~70 min)	Intermittent dosing (recovery ~30 min)	Initial dose with 15-min Infusion (recovery ~20 min)
Adult	1.5 mg/kg	1 mg/kg + 0.5 mg/kg at 10 min	0.25 mg/kg + 2.5 mg/kg/h
12 years	1.75 mg/kg	1 mg/kg + 0.5 mg/kg at 8 min	0.275 mg/kg + 2.75 mg/kg/h
6 years	2 mg/kg	1.25 mg/kg + 0.625 mg/kg at 8 min	0.3 mg/kg + 3 mg/kg/h
2 years	2.125 mg/kg	1.5 mg/kg + 0.75 mg/kg at 8 min or 1 mg/kg + 0.5 mg/kg at 6 min + 0.5 mg/kg at 10 min	0.35 mg/kg + 3.5 mg/kg/h

Concern has been raised that very rapid intravenous administration of ketamine may increase the risk for apnea or marked respiratory depression, presumably due to rapid changes in brain ketamine concentrations [79, 251]. However, in the author's practice, small intravenous doses of 0.25–0.5 mg/kg administered over less than 5 s have not been associated with adverse respiratory effects and can provide effective PSA for procedures lasting for less than 5 min, such as simple fracture reductions or abscess incision and drainage (I&D).

Indications: Ketamine is particularly effective as PSA for intensely painful procedures such as fracture reduction, dislocated joint reduction, burn debridement, or abscess I&D [9, 159]. Ketamine

is also an effective PSA technique for brief painful radiological procedures such as guided joint aspiration or nonpainful CT scans, and repair of complex lacerations. Procedures that involve the oropharynx, such as peritonsilar abscess I&D, or endoscopy may be performed with light ketamine sedation (see case examples) but the sedating physicians must be prepared for an increased risk of laryngospasm [146, 318, 319].

Dosages: When administered in doses greater than 2 mg/kg, ketamine readily induces general anesthesia with unresponsiveness to painful stimuli yet with continued spontaneous respirations and good cardiac output. However, initial intravenous doses ≥2.5 mg/kg or total dose ≥5.0 mg/kg after repeated dosing have been associated with increased risk of adverse respiratory events [137]. It is recommended that ketamine be titrated to the desired degree of blunted response to intense pain. Complete lack of responsiveness to painful stimuli is unnecessary with ketamine as it is a potent amnestic agent [9, 79]. Providers and parents can be reassured (but not guaranteed) that most patients will have little or no memory of the painful procedure, even if moans occur during the most painful parts. It helps parents if providers confirm procedural amnesia by asking the patient what is remembered after recovery, especially when the parents have remained in the room during the procedure.

IV: (see Section "Pharmacokinetic") total dose 1–2 mg/kg when used alone is sufficient for the most intensely painful procedures lasting less than 5–15 min. If coadministered with midazolam, 1–1.5 mg/kg is often sufficient. The total dose can safely be administered as a single dose over 30–60 s but many sedators begin with an initial dose of 0.5 mg/kg administered over 15–30 s and repeated every minute until the desired blunted response to pain is achieved. For prolonged procedures, additional doses of 0.25–0.5 mg/kg may be administered as needed (about every 5–10 min), depending on individual patient response to stimulus [9, 315]. The smaller initial dose with additional doses as needed may shorten time for recovery [160]. Use of local anesthetics, when applicable, is highly encouraged to decrease the amount of ketamine needed. For an intensely painful but very brief procedure in which patient movement can be tolerated, e.g., moving a patient with a femur fracture off the spine board onto the ED bed, a small dose (0.2–0.3 mg/kg) administered rapidly by IV (over less than 5 s) can enable the patient to tolerate the procedure without losing consciousness; patients should be warned of feeling "weird" and monitored for possible sedation with this technique.

IM: 2–4 mg/kg, with smaller dose used for brief procedures in which local anesthesia is also used, e.g., laceration repair [316, 320].

Onset/duration:

IV: sedation-analgesia within 15–30 s with initial deeper effects lasting 5–10 min and recovery by 60 min, depending upon dose administered.

IM: sedation-analgesia within 5–15 min, duration 30–150 min, depending upon dose administered.

Metabolization: Hepatic degradation of ketamine within the cytochrome systems results in norketamine, which has one third the analgesic potency of ketamine. Norketamine has a shorter elimination half-life (1.13 h) than ketamine (2.1 h) [321].

Pregnancy category B

Adjuncts

Glycopyrrolate (Robinul®)

Indication: Antisialagogue is used by some clinicians before initial dose of ketamine. Preferred by some over atropine because it does not cross the blood–brain barrier thus, not causing possible undesirable CNS effects. Antisialagogues prior to single doses of 1–2 mg/kg of ketamine are likely unnecessary [137, 143, 144, 251]. It is unclear whether use of antisialagogues are beneficial in children with active URIs. Many children complain of "cotton mouth" for 6–8 h after glycopyrrolate administration [9].

Concentration: 200 μg/mL.

Dose: 5 μg/kg IV. Maximum dose is 200 μg. Administer at least 5–15 min before the initial dose of ketamine.

Atropine

Indication: Antisialagogue used by some clinicians in conjunction with initial dose of ketamine (instead of glycopyrrolate). Concern has been raised about potential CNS adverse effects with atropine, e.g., excitation, but this appears uncommon [143]. Antisialagogues prior to single doses of 1–2 mg/kg of ketamine are likely unnecessary [137, 143, 144, 251]. It is unclear whether use of antisialagogues are beneficial in children with active URIs.

Dose: 0.01 mg/kg (minimum 0.1 mg, maximum 0.5 mg).

Nitrous Oxide (N_2O)

Nitrous oxide (N_2O) is a colorless, odorless, and tasteless gas that, in a linear dose-response pattern, induces dissociative euphoria, drowsiness, anxiolysis, and mild to moderate amnesia and analgesia with onset and offset of effects within 2–5 min [322, 323]. N_2O is blended with oxygen (N_2O/O_2) and typically is described by the N_2O component, e.g., "70% N_2O" is 70% N_2O+30% O_2 [324]. At a specific concentration of N_2O, however, depth of sedation can vary considerably. One study of N_2O for ED PSA found 90% of children receiving 50–70% N_2O were mildly sedated (drowsy, eyes open or closed, but easily aroused to consciousness with verbal stimulus), whereas moderate or deep sedation occurred in 3% receiving 70% N_2O and in none receiving 50% [325]. Others report 2–10% of children may be poorly sedated during ED PSA with N_2O [10, 325, 326].

Since N_2O sedation and analgesia are usually mild to moderate, children are partially aware and strategies to enhance the gas's anxiolytic, dissociative, and euphoric effects are vital to successful use for PSA. Guided imagery significantly augments N_2O's efficacy and helps allay anxiety [323, 327]. Children naïve to intoxication are frequently frightened by the floating or tingling sensations caused by the gas, but they readily accept these effects when incorporated into non-frightening scenarios. The author often encourages preschool and school-aged children to imagine flying to a favorite or imaginary place, "soaring with eagles, past clouds and stars to check out the moon," guiding the child during the sedation by detailed descriptions of what might be "seen" along the way. Alternatively, some children like describing their own imaginings, allowing the author to figuratively "tag along," as with a 5-year-old girl who portrayed in great detail her "chocolate ponies" as her radius fracture was being reduced. Finally, some older children and teenagers prefer the partial awareness with N_2O sedation as they, like many adults, fear loss of vigilance or control associated with potent sedation or anesthesia.

Effective pain reduction by concurrent use of local anesthesia and/or systemic analgesia for painful procedures is also crucial for successful N_2O ED PSA [328]. For examples, forearm fractures can be reduced with minimal distress when N_2O sedation is augmented by a lidocaine hematoma block [88, 329, 330], or lacerations repaired calmly in young children when they have also received topical anesthetic [10]. The lack of painful administration or need for venous access and the rapid onset and offset of effects make N_2O ED PSA an attractive option for many clinical situations.

N_2O can safely be administered by specially trained nurses to healthy children for ED PSA [62, 331, 332].

Indications: N_2O, along with local anesthesia and/or oral analgesics, primarily is used for anxiolysis, mild analgesia and amnesia during brief (<5–10 min) procedures, such as laceration repair, abscess incision and drainage, lumbar puncture, IV placement, and some fracture reductions. Use of 60–70% N_2O or coadministration of opioids or sedatives may deepen sedation and improve efficacy [129–131]. The author frequently administers oxycodone 0.2–0.3 mg/kg orally 30–60 min prior to N_2O sedation for I&D of an abscess in toddler and preschool children. Although seldom seen, these children are monitored for respiratory depression before, during, and after the sedation.

Many find the gas more effective in children old enough to cooperate and use imagination, but significant reduction of procedure-related distress

has been observed in 2 year old and younger children [10]. In the author's ED, N_2O sedation is regularly used effectively in infants of 3 months of age and older by administering with a continuous-flow system, described later.

Suturing-related distress in children can be reduced by N_2O [10, 326, 333–335]. We found 2–6 year old children who had received topical anesthetic and were viewing cartoons with a parent at the bedside, had less distress during wound cleaning, supplemental lidocaine injection, and suturing if receiving 50% N_2O instead of oral midazolam. Children who received N_2O alone recovered rapidly without ataxia or dizziness, but did have more vomiting (10%) [10]. Of note, 30% N_2O was found insufficient in children younger than 8 years old in another study [333].

Mid to distal forearm fracture reduction can be effectively performed with N_2O sedation, particularly when combined with a local anesthetic hematoma block [88, 329, 330, 336–338]. We found N_2O plus 1% lidocaine hematoma block (2.5 mg/kg, maximum 100 mg) as effective as intravenous ketamine in reducing distress during fracture reductions in children aged 5–17 years. This technique is often most effective in displaced mid to distal forearm fractures which have large fracture site hematomas that enable effective hematoma blocks, whereas, torus or green-stick fractures that require reduction likely have small or no fracture hematomas making the lidocaine block less effective; an effective fracture hematoma block is the key for maximum success. For these incomplete fractures, hematoma blocks may provide partial pain relief and, combined with 70% nitrous oxide along with prior oral oxycodone or other potent analgesic, enable many children to tolerate fracture reduction with acceptable distress. The child usually recalls less pain related to the fracture reduction performed with N_2O sedation than an observer would expect based upon the child's response during the procedure [329]. It is usually reassuring to ask the child after recovery, with the parent(s) present, what he or she recalls of the procedure, especially when the parent was present during the reduction and the child had manifested some distress. Recovery is markedly faster from N_2O compared to ketamine-based sedation for fracture reduction (16 vs. 83 min) [88]. If the N_2O is turned off as soon as any painful moulding of the cast at the fracture site after reduction is completed, the patient is typically recovered to near baseline before the casting or splinting is finished.

Children's distress during other painful ED and outpatient procedures such as lumbar puncture, abscess drainage, dressing change, and intravenous catheter placement likewise can be reduced by N_2O [325, 335, 339–344]. Recovery from N_2O sedation typically is very rapid, with the child able to sit alone within 5 min and ready for discharge within 15 min [76].

Technique: As described previously, successful N_2O sedators engage the child in imaginative stories throughout the procedure. Distraction, imagery, and storytelling significantly enhance desired effects by giving the child a nonthreating construct in which to place the sensations caused by the gas. While breathing N_2O, children are able to follow commands, describe sensations of floating, frequently laugh, and occasionally chew or lick masks that have been scented with bubblegum spray or flavored lip-balm to enhance acceptance of the mask. Adolescent and school-aged children often begin giggling if it is suggested to them that this is expected and their parents typically also begin laughing when this occurs, presumably easing their own anxiety. Coaxing children as young as 2 years of age to hold the mask on their face adds a measure of safety by allowing them to remove the mask quickly if vomiting occurs. Their ability to hold the mask also indicates their depth of sedation and may reduce anxiety related to the mask covering their mouth/nose. When the mask is held in place by a sedator, that person must be vigilant for evidence of vomiting and quickly remove the mask to allow the child to clear the emesis.

Titration of the gas beginning at 30%, the anxiolytic dose, and increasing the concentration to 50–70% over 2 min may reduce children's fear during induction. Others find when children have been prepared with explanations about what effects they are likely to feel, they tolerate beginning at 50–70%. With either technique, the child should breathe the maximum concentration

desired for 1–2 min, allowing full effect, before beginning the procedure.

Administration of 100% oxygen after cessation of N_2O to prevent "diffusion hypoxia" is unnecessary unless the patient is emerging from deep sedation or general anesthesia. N_2O diffusing from the bloodstream into the alveoli and displacing oxygen is readily exhaled without causing hypoxia in patients recovering from sedation with N_2O alone [128, 345, 346]. As with any sedation technique, children should be monitored with pulse oximetry until alert, usually less than 3–5 min after ending N_2O administration.

Delivery system: Until recently, delivery of N_2O (fixed at 50%) in the ED has been by demand-valve systems designed for adult use (Nitronox/Entonox®). Children have difficulty generating the negative inspiratory pressure required to initiate gas flow with these devices. Continuous-flow systems, such as those used by dentists, oral surgeons, and anesthesiologists, in contrast, provide free flow of gases with the ability to deliver up to 70% N_2O. These systems allow normal respirations and are easily used by patients of all ages [324, 347]. Dental systems with nasal hoods can be adapted for use with a full face-mask by adding into the expiratory limb an open gas interface designed for anesthesia machines. N_2O concentration is limited to a maximum of 70–75% as concentrations exceeding 79% (+21% O_2) would cause hypoxia. Accidental administration of 100% N_2O due to machine or system failure can be rapidly lethal [154, 348, 349]. Providers must be very familiar with the mechanisms of the N_2O delivery system used. A machine or systems check should be performed before each use of N_2O to assure proper function of the machine and monitors.

A scavenging device should be an integral part of the delivery system to minimize ambient levels of N_2O gas exposure to healthcare workers since chronic and repeated exposure to N_2O may cause abnormalities in hematologic, neurologic, and reproductive systems (see cautions). The N_2O delivery device and the treatment area in which it is used should be in compliance with National Institute of Occupational Safety and Health Standards and state safety guidelines and regulations [350]. It is beneficial to have room air exchanges of at least 10–20/h in treatment rooms to remove any N_2O that has escaped the scavenging process.

Monitoring: An in-line oxygen analyzer should be used to assure proper equipment functioning/adequate oxygen delivery during N_2O administration [154]. A gas analyzer that measures inspiratory and expiratory N_2O and end-tidal CO_2 concentrations adds additional assurance of patient safety and equipment function.

Administration of ≤50% N_2O, without any other sedative, narcotic, or other respiratory depressant drug, to children ASA-PS class I or II, is considered minimal sedation and the patient may be monitored by direct visualization and intermittent assessment of their level of sedation [154]. The child should be able to be verbally interactive throughout the sedation. If >50% N_2O is administered or if the patient receives concurrent narcotic or other sedative drugs, the patient should be observed closely for moderate sedation and monitoring should escalate accordingly with pulse oximetry, etc. Since oxygen is blended with N_2O, even mild hypoxemia is very unlikely and should cause immediate investigation to determine the cause.

Contraindications/cautions: At normal atmospheric pressure, N_2O cannot induce general anesthesia, unless combined with other agents. N_2O at 30–70% has been safely used widely for more than a century to reduce distress in children during dental procedures [351]. Review of nearly 36,000 administrations of 50% N_2O for non-dental procedures, 82% of which were in children, found 9 (0.03%) serious adverse events (somnolence, vomiting, bradycardia, vertigo, headache, nightmares, sweating) that may have been attributed to the N_2O [352]. In healthy patients (ASA-PS I, II), N_2O has minimal cardiovascular or respiratory effects [76, 130, 345]. N_2O, however, may enhance the depressed response to hypoxia and hypercarbia induced by other agents [129–131, 325, 353].

N_2O diffuses rapidly into air-filled cavities causing volume and or pressure increases proportional to concentration and duration of N_2O inhaled. Therefore, N_2O should not be administered to patients with areas of trapped gas such as pneumothorax, obstructive pulmonary disease, or

bowel obstruction. Albeit seemingly rare, patients with acute otitis media may experience painful increase in middle ear pressure. Other relative contraindications include significant head injury (N_2O mildly increases intracranial blood flow), altered mental status, and psychiatric disorder (N_2O may cause dysphoric effects similar to ketamine).

Bone marrow suppression, liver, CNS, and testicular dysfunction, decreased fertility and increased spontaneous fetal loss, and peripheral neuropathy may possibly occur with repeated and chronic exposure [76, 324]. None of these adverse effects have been found when scavenging devices are integrated into the system. Therefore, use of a scavenging device is essential to minimize ambient levels of gas and exposure to healthcare workers.

Deaths associated with N_2O use have been due to inadvertent administration of 100% nitrous oxide, with subsequent hypoxia [348, 349]. These occurrences primarily were in patients already sedated with other drugs as part of anesthetic regimens. These tragedies point out the essential need for clinicians to understand all aspects, including mechanical, of the gas delivery device being used.

Pregnancy category C

Adverse effects: Vomiting occurs in approximately 10% of children receiving 50% N_2O, along with transient dizziness and headache in some [76]. These effects usually resolve within 5 min of cessation of N_2O administration. Vomiting frequency increases with opiate and decreases with midazolam coadministration [10, 88]. Some providers believe the risk of vomiting increases when the duration of administration exceeds 5–10 min, especially with greater than 50% concentrations, but this is yet to be substantiated. Whether antiemetics such as ondansetron reduce N_2O induced nausea and vomiting is unclear. Protective airway reflexes are largely intact when N_2O is used alone [354–356]. Whether combining N_2O with other sedatives or analgesics increases risk for aspiration and other adverse events is unknown but the risk likely correlates with the patient's depth of sedation and effects of the coadministered drug.

Dosages: Concentrations of 30–50%, blended with oxygen, achieve Minimal to light Moderate sedation in most children without adverse cardiopulmonary effects [76]. More recently, routine use of 60–70% has been recommended and found safe in children undergoing sedation in the ED [325]. In the author's ED, 50–70% concentrations are typically used with initial higher concentrations and then reduced as the most painful part of the procedure is accomplished.

Onset/duration: Patients experience the effects of N_2O within 1 min but for optimum effect they should inhale the gas for 2–3 min before beginning a procedure to allow brain concentrations to equilibrate with the delivered concentration of gas. Recovery occurs rapidly with children being able to sit alone by 3–5 min after cessation but initially they should be assisted with walking as ataxia may occur for a bit longer.

Mechanism of action: N_2O has *N*-methyl-d-aspartate (NMDA) glutamate receptor antagonist, opioid agonist, and GABAergic effects [357–359].

Metabolization: N_2O is excreted unchanged by exhalation.

Ketamine+Midazolam or Fentanyl+Midazolam Techniques for Deep Sedation

Providers utilizing these regimens should be thoroughly familiar with these medications and sedation guidelines outlined in text. Sedation should be performed in an area fully equipped for resuscitation.

Pre-Sedation Assessment and Preparation

1. Initial assessment: determine patient's ASA classification, airway risks, time of last oral intake, obtain informed consent.
2. Establish indwelling venous access maintained with normal saline or Ringer's lactate.
3. Attach patient monitors to continuously measure patient's oxygen saturation (with variable

pitch indicator), heart rate, and respiratory rate and intermittently measure blood pressure. Consider pre-oxygenation and supplemental oxygen delivery during the sedation if capnography if available and staff trained in use.
4. Prepare positive-pressure ventilation bag and mask, assure ability to deliver supplemental oxygen.
5. Prepare oral suctioning device with rigid tip.

During Sedation

1. Assign a provider whose sole responsibility is to monitor patient safety.
2. Continuously monitor patient by direct observation, oxygen saturation (with variable pitch indicator), HR, RR, and monitor blood pressure after each medication infusion and at 5-min intervals. Patient monitoring and direct observation at increasing intervals is continued during recovery until discharge criteria are met.
3. Infuse medications near the hub of the catheter over 10–20 s, in small incremental doses to titrate to desired endpoint of analgesia, sedation. Use of dilute solutions and precalculated dosage tables based upon patient weight is recommended.
4. Administer medications intravenously when supportive staff present and prepared to render support if necessary and provider to perform procedure prepared to begin.

Fentanyl Technique

(a) Midazolam: 0.05–0.1 mg/kg (0.05–0.1 mL/kg) at 2–3 min intervals; endpoint: decreased patient anxiety, mildly slurred speech, drooping eyelids; typically effective dose: not more than 0.1 mg/kg to induce marked amnesia along with sedation. Then
(b) Fentanyl (10 μg/mL): 0.5 μg/kg (0.05 mL/kg) at 2–3 min intervals; endpoint: decreased patient responsiveness to painful stimulus or decreasing oxygen saturations; typically effective dose: 1–1.5 μg/kg.

Ketamine Technique

(a) Midazolam may be reserved for anxious patients undergoing ketamine sedation. For anxiolysis, dose: 0.05 mg/kg, maximum dose: 2 mg, single administration 5–15 min prior to initiation of sedation.
(b) Ketamine (10 mg/mL): dose: 0.5–1 mg/kg (0.05–0.1 mL/kg) at 1 min intervals; endpoint: decreased patient responsiveness to painful stimulus; typically effective dose: 1–2 mg/kg. Supplemental doses of 0.5 mg/kg may be administered as indicated by patient distress.

Consider using an antisialagogue, e.g., glycopyrrolate 5 μg/kg or atropine 0.01–0.02 mg/kg, prior to ketamine administration if it is an anticipated procedure will require multiple supplemental doses of ketamine.

Caution: Suggested doses may readily result in oxygen saturation falling below 90% in patient's breathing room air, particularly when fentanyl is used. Providers must be prepared to immediately turn the patient to his side if vomiting, reposition or suction patient's airway, provide supplemental oxygen or positive-pressure ventilation until patient has returned to baseline physiologic status and recovered from sedation.

Final Thoughts

This chapter has presented the sedation provider with a range of sedation techniques and options for painful and non-painful procedures which may need to be performed on an urgent basis. There is no doubt that sedation and analgesia are important components of the emergency department care and should be an integral component of the emergency medicine physician's practice. The training and credentialing process for sedation is an area of recent interest from the American College of Emergency Physicians. In July 2011, the American College of Emergency Physicians released a Policy statement entitled Procedural Sedation and Analgesia in the Emergency Department: Recommendations for Physician Credentialing, Privileging, and Practice [362]. This Policy iterated that the chief of the emergency medicine service at each institution will be responsible for establishing criteria for credentialing and recommending emergency physicians for sedation privileges. Sedation training should "focus on the unique ED environment". This

Policy is important, because it empowers the chief of emergency medicine with the responsibility of establishing sedation training and credentialing requirements for the emergency medicine specialty. Furthermore, the Policy expands the role of the emergency physicians as well as emergency medicine nurses by condoning the capability of qualified ED nurses to "administer propofol, ketamine, and other sedatives under the direct supervision of a privileged emergency physician". The Policy also recognizes that there may be occasions whereby the emergency medicine environment may not lend itself to having a separate physician administer the sedative and another to perform the procedure: For these situations, the Policy states "Deep sedation may be accomplished…..by the same emergency physician both administering sedation and performing the procedure".

As the practice of sedation evolves, one can anticipate that the American College of Emergency Physicians will continue to survey the landscape, evaluate the literature and recommend policies and guidelines to promote the safe and efficacious delivery of sedation in the emergency medicine environment.

Case Studies

Case 1

A 12 year-old boy has closed *displaced metaphyseal fractures of his distal right radius and ulna* and numbness in his 3rd and 4th fingers. He fell 30 min ago running in gym class and has no other injury. He takes methylphenidate for attention deficit-hyperactivity disorder. He otherwise is healthy and has never received sedation or anesthesia. He ate lunch 2 h prior to arrival and was given ibuprofen by his mother on the way to the hospital. He is anxious and crying in triage.

Issues: Pain relief now and during radiographs and exams; PSA for fracture reduction with consideration of his fasting status, anxiety, ADHD, and neurovascular status of his injury.

1. *Pain relief* will facilitate imaging of the fractures, accurate assessment of the injury, and preparation of the patient for PSA for fracture reduction. Options include:
   (a) *Splinting* the injured area to prevent movement of the fractured bones provides significant pain relief.
   (b) *Systemic analgesia*: Administer before radiographs, even if the child indicates less pain after splinting. Repositioning of the injured limb for radiographs and subsequent exams will be quite painful. Options include:
   (i) *Oxycodone orally*: In our ED, nurses follow standing orders to administer a first dose of oxycodone 0.2 mg/kg orally (maximum dose 10 mg) in triage to children with a potential isolated extremity fracture or other painful injury. This allows rapid and effective attention to the reduction of pain and high patient, family, and staff satisfaction. Noticeable analgesia occurs by 20–45 min with peak effect by an hour and with duration of 2–4 h. This dose is unlikely to cause sedation in children with painful injuries. Doses for home use are 0.05–0.15 mg/kg. Oxycodone is preferred over codeine because it does not require metabolic conversion for analgesic effect. Codeine is slowly or poorly converted to morphine in 2–40% of patients and thus

provides poor or no pain relief to such children. If codeine previously has been effective for a specific child, a first dose of codeine 2 mg/kg orally is effective for these painful injuries with subsequent or home doses of 1 mg/kg.

(ii) *Fentanyl intranasally,* 1.5–2 μg/kg, achieves significant pain relief within 5–10 min with duration of 30–90 min. Use atomizer to spray small volumes of concentrated intravenous fentanyl solution (50 μg/mL) to improve absorption. Divide total dose into repeated sprays of ~0.1–0.2 mL/nostril. Use of small volumes reduces drainage of drug into posterior pharynx where it is less absorbed. If a wide margin of safety is determined after more extensive use of this technique, it might be performed by nurses in triage, but currently it is performed by a physician in a treatment room with patient monitoring for respiratory depression.

(iii) *Opioids intravenously* titrated to effect will provide the greatest pain relief. Fentanyl 1–2 μg/kg IV will provide analgesia within 1–2 min, lasting 30–60 min, whereas morphine 0.1 mg/kg IV will provide initial analgesia within 5–10 min with peak effect at 10–20 min and lasting 2–3 h. This strategy requires IV insertion, typically in a treatment room after physician assessment and orders. Anxiety and pain associated with catheter insertion are significant for many children and are greatly reduced by use of local anesthesia such as buffered lidocaine injected subcutaneously via a 30 gauge needle at the site of insertion.

(iv) *Nitrous oxide 50–70%* provides rapid pain relief. However, because continued analgesia requires ongoing administration and N_2O scavenging systems are not mobile, a longer acting systemic analgesic usually is needed. One strategy is to use N_2O to reduce the patient's pain and distress while an IV catheter is inserted for subsequent opioid administration. This strategy typically requires physician assessment and orders, access to N_2O, and IV catheter insertion in a treatment room.

2. *Fasting status*: This child ate lunch 2 h prior to his arrival. Pain from injury and opioid analgesics unpredictably slow intestinal motility. It is uncertain if delaying sedation for 2–4 h in these patients will allow significant additional gastric emptying. Vomiting with PSA does not correlate with the length of fasting. Furthermore, ED PSA does not involve tracheal intubation, a procedure that significantly increases risk of pulmonary aspiration during general anesthesia. Of note, pulmonary aspiration has not been reported in children undergoing ED PSA, despite most being incompletely fasted. As with general anesthesia, no studies have determined if pulmonary aspiration risk is reduced in non-fasted patients by pre-sedation administration of medications to enhance gastric emptying, inhibit gastric acid production, or decrease pH of gastric contents and such strategies are not recommended. The author's practice is to use PSA techniques that preserve airway reflexes as described herein, to be prepared for vomiting in all patients, and to perform PSA when the full complement of providers is available to perform the procedure and monitor the patient.
3. *PSA techniques*: Since this non-fasted patient has potentially increased risk of pulmonary aspiration of gastric contents, a

sedation technique that better preserves protective airway reflexes may increase patient safety. Ketamine and N_2O are NMDA receptor antagonists that blunt protective airway reflexes less than the opioid and GABAergic agents such as fentanyl, midazolam, and propofol.

(a) *Nitrous oxide* (*50–70%*) *plus lidocaine fracture hematoma block,* along with oxycodone administered at triage, is as effective in reducing distress associated with fracture reduction as intravenous ketamine, provided an effective hematoma block is placed. To reduce risk of nerve and vascular injury from injection, hematoma blocks are typically reserved for mid to distal forearm, and, occasionally, ankle fractures. We administer 50% N_2O to the child as the orthopedic surgeon, using sterile technique and a dorsal approach, injects 1% buffered lidocaine (2.5 mg/kg or 0.25 mL/kg, maximum dose 100 mg or 10 mL) into the fracture hematoma. N_2O 70% is usually administered for the subsequent fracture reduction. Aspiration of hematoma blood into the lidocaine-containing syringe confirms proper location of the needle for injection. Perhaps counterintuitively, the worse the fracture, the more effective is fracture site anesthesia due to larger hematomas. The provider must be prepared for as yet unreported but potential seizure or dysrhythmia due to rapid intraosseous absorption of lidocaine. This theoretical risk is low since the injected lidocaine is within the drug's therapeutic dose range. Some orthopedic surgeons prefer not to use this technique if the fracture and swelling cause numbness in the hand, typically median nerve distribution, because of inability to reassess nerve function immediately postreduction. Use of lidocaine instead of longer acting local anesthetics such as bupivacaine enables postreduction neurologic assessment within 1–2 h. Variable patient awareness is present with N_2O PSA, thus distraction and guided imagery are crucial to improve efficacy of this technique. Some older children and teenagers, as many adults, prefer not to be unconscious during a procedure if pain is sufficiently reduced.

(b) *Ketamine I.V. with or without Midazolam* more effectively reduces patient distress during intensely painful procedures and causes less respiratory depression than fentanyl or propofol-based techniques. Intravenous administration is preferred because multiple attempts likely will be needed to align both the radius and ulna, thus increasing potential need for additional doses of ketamine. Time of recovery is reduced by administering a smaller initial dose followed by a half dose. For a child of this age, an *initial ketamine dose 1 mg/kg followed by 0.5 mg/kg at 8 min* likely results in approximately 15 min of very deep sedation with recovery to drowsiness and easy arousal by verbal stimulation by about 30 min. If longer deep sedation is needed for repeated reduction attempts, additional dose of 0.5 mg/kg can be given as needed. Alternatively, an initial ketamine dose of 1.75 mg/kg will result in 15 min of deep sedation but recovery likely will take 60–70 min.

Intramuscular ketamine 4 mg/kg provides effective PSA without vascular access but additional doses, if necessary, will require 4–5 min to determine if sufficient. Recovery is significantly longer than with intravenous ketamine and vomiting is more frequent (26 vs. 12%). Ability to obtain vascular access emergently (intraosseous, if necessary) must be present to manage life-threatening adverse events should they occur.

Midazolam 2 mg total dose may reduce the child's anxiety as preparations are made for PSA. Although yet unconfirmed with PSA, reduced anxiety at induction correlates with reduced dysphoria during recovery from general anesthesia. This small dose is not likely to cause respiratory depression or prolong recovery. Midazolam administered in the same syringe or immediately after ketamine does not appear to reduce recovery dysphoria.

Glycopyrrolate or atropine to reduce ketamine associated increased salivation are recommended by some to reduce the low risk of laryngospasm. Hypersalivation is usually not significant with these doses of ketamine but may occur with repeated doses for prolonged procedures. The author no longer routinely administers an antisialagogue because these agents have been associated with increased likelihood of adverse respiratory events, and patients complain of dry mouth after recovery.

Vomiting: Administration of opioids such as morphine or oxycodone with ketamine increases emesis (10 vs. 25%) whereas, administration of midazolam decreases vomiting (19 vs. 10%) as does ondansetron (13 vs. 5%).

Cautions: Although unlikely to occur, providers must be prepared for hypoventilation, apnea, or laryngospasm with ketamine. As with all deep sedations, this child must be monitored for adverse effects by an experienced dedicated provider during induction, sedation, and recovery. If vomiting occurs, the procedure immediately is interrupted and the child turned to his side to assist his clearing emesis. Observers, e.g., parents, should be forewarned about nystagmus and catatonic stare during sedation and possible dysphoria during recovery. Similarly, patients should be prepared for possible diplopia, dizziness, hallucinations, and a brief period of blindness during recovery. Getting the child to focus on pleasant thoughts during induction and recovery may reduce some of these psychotomimetic effects. Most patients will have no memory of even intensely painful procedures, even if they occasionally moan, but some will have partial recall, usually quite vague. It may help reassure observers if the child indicates no recall when asked after recovery.

(c) *Fentanyl + Midazolam or Propofol* provides effective PSA but blunts protective airway reflexes more than ketamine. This child's recent food intake makes these techniques less desirable. It is unknown whether delaying PSA will improve gastric emptying. Please see *Fasting Status* mentioned previously.

(d) *Reduction under general anesthesia* may be considered. However, reduction should not be delayed long because of the apparent median nerve impingement. Of interest, general anesthesia with endotracheal intubation in non-fasted children may have greater risk of pulmonary aspiration than ED PSA.

Case 2

A 5-year-old girl has a closed *distal radius fracture*, dorsally angulated 30° but hinged at the cortex. She gets "car sick" and had multiple episodes of vomiting after an operation last year.

Issues: Pain management, history of motion sickness, and postanesthesia vomiting, and optimum technique for a painful but brief fracture reduction. Of note, in young children, some orthopedic surgeons do not reduce metaphyseal fractures "minimally displaced" in the primary plane of motion because they will remodel to normal over the coming months. Standardized determination of how much

displacement will successfully remodel remains to be developed.

1. *Pain relief*: please see Case 1. Splinting and oral oxycodone likely are sufficient.
2. *PSA technique options*: Since this fracture reduction will take "one brief but painful push," effective local anesthesia or brief deep sedation with rapid recovery is desirable.
   (a) *Nitrous oxide* (*50–70%*) *plus fracture hematoma lidocaine block*: This fracture may not have a significant hematoma, thus reducing the effectiveness of a hematoma block. Combining 70% N_2O with oxycodone, 0.2 mg/kg orally without the hematoma block, may provide sufficient analgesia and partial amnesia for remaining pain. N_2O should be administered for at least 2 min prior to reduction to maximize the gas's effects. Balancing potentially incomplete PSA against the benefits of not needing vascular access and rapid recovery should be discussed with the parents. A downside to this technique is the 25% likelihood of vomiting when N_2O is coadministered with an opioid. Coadministration of oral midazolam with N_2O (without oxycodone) reduces vomiting but prolongs recovery. It is unknown if oral ondansetron significantly reduces vomiting with N_2O and oxycodone.
   (b) *Ketamine with or without Midazolam intravenously*: Since this fracture reduction will likely be very brief, experienced providers may consider *rapid administration* of *ketamine 0.5–0.75 mg/kg* (pushed over 3–5 s) to induce about 5 min of deep sedation, with additional ketamine given if necessary. The performer of the fracture reduction should be ready as the ketamine is infused. With the single small rapid dose, deep sedation will occur within 1 min and recovery to being drowsy but responsive to verbal stimulation will occur by 10–15 min, often as casting is completed. Alternatively, administered over 30–60 s, ketamine 1.25 mg/kg provides deep sedation for 10–15 min with recovery by about 30 min or ketamine 2 mg/kg provides deep sedation for 15 min with recovery by an hour. *Vomiting* frequency after small dose ketamine is unknown. See Case 1 for additional information.

   Intramuscular ketamine 4 mg/kg provides effective PSA but recovery is significantly longer than with intravenous ketamine. See Case 1 for additional information.
   (c) *Fentanyl with Propofol or Midazolam* intravenously provides effective PSA for fracture reduction but with more respiratory depression than ketamine techniques (desaturation to less than 90% in approximately 25%-FM vs. 20%-FP vs. 5%-KM). Since respiratory depression/apnea occur frequently, providers should be experienced with this technique and well prepared to provide ventilatory support. Vomiting is less frequent with propofol than ketamine-based techniques. Recovery is faster with propofol/fentanyl than with ketamine/midazolam-based PSA (23 vs. 33 min in one study), especially if repeated doses are needed. Recovery is described as more pleasant after propofol sedation compared to ketamine. Time to discharge after fentanyl/midazolam is similar to that of ketamine/midazolam.

Case 3

A 3-year-old boy has blistering *hot water burns* to his right face and much of his anterior chest and abdomen, sustained when he pulled a pot with boiled water off the stove top. He was transported to the ED by EMS who was unable to insert an IV catheter, in part due to the child's obesity (weight 23 kg). The child has a history of mild asthma without hospitalization, controlled with albuterol MDI

as needed. He has had a runny nose and cough without fever for 1–2 days; his usual snoring while sleeping has worsened with the URI. The child is crying loudly and coughing as he is placed in a treatment room. Good air exchange with expiratory wheezes bilaterally is noted on auscultation.

Issues: rapid pain relief, difficult vascular access, obesity, history of snoring, asthma with current wheezing, and upper respiratory infection.

1. Rapid pain relief options:
   (a) *Fentanyl intranasally* 1.5–2 μg/kg, achieves significant pain relief within 5–10 min. See Case 1 for additional information. Base dose on estimated lean body weight (~15 kg for 3 year old); initial 2 μg/kg dose for this child is 30 μg or 0.6 mL. Divide the 0.6 mL total dose into four sprays of ~0.15 mL/nostril. The impact of an acute URI upon transmucosal absorption is unclear.
   (b) *Nitrous oxide 50–70%* will provide rapid pain relief, but its analgesic effect is lost within minutes when the gas is stopped. N_2O can be administered while IV catheter insertion is attempted. Use of a continuous circuit or N_2O delivery system easily activated by a young child is necessary.
   (c) *Oxycodone orally*, or other potent oral analgesic, will provide pain relief but onset is 20–40 min. For this young patient with a very painful injury, an initial oxycodone dose of 0.3 mg/kg is given orally, based on estimated lean body weight of 15 kg it is 4–4.5 mg. This dose may result in mild sedation as pain relief is achieved. See Case #1 for additional information.
   (d) *Opioids intravenously* titrated to effect will provide the greatest pain relief, if vascular access can be achieved. Fentanyl 1–2 μg/kg will provide analgesia within 1–2 min, lasting 30–60 min, whereas morphine 0.1 mg/kg will provide initial analgesia within 5–10 min with peak effect at 10–20 min and lasting 2–3 h.
   (e) *Intramuscular ketamine* 4 mg/kg provides rapid and marked pain relief and PSA without vascular access. Please see Case 1(b) for further information. If providers are available to monitor the patient and begin debridement, this may be a reasonable option. The greatest risk with this technique is that emergent vascular access to manage a life-threatening adverse event such as laryngospasm would be difficult, but an intraosseous needle could be placed, if necessary. IV catheter insertion for ongoing care can be attempted concurrently with the burn debridement.
2. *Difficult vascular access*: *Buffered lidocaine injected subcutaneously* with a 30 gauge needle provides nearly painless rapid local anesthesia for IV insertion. Use of this or other local anesthetic technique in this obese child will be especially important because multiple attempts likely will be needed. Because of the prolonged onset, topical anesthetic creams are not an optimum choice for local anesthesia. If available, *N_2O 50–70%* will reduce IV insertion-related distress as well as provide systemic analgesia as described in (b).
3. *Obesity, snoring*: As noted earlier, determine medication doses upon estimated lean body weight. Since fat is less perfused than brain and muscle, doses based upon total weight will result in higher initial plasma and brain concentrations and greater risk of adverse effects, and prolonged recovery. Obesity also reduces lung functional residual capacity, increasing his risk of hypoxia with respiratory depression, and increases likelihood of upper airway obstruction as indicated by his history of snoring. Use of supplemental oxygen during sedation of this patient will provide a greater margin of safety by prolonging the time to hypoxia if decreased ventilation occurs. Monitoring with end-tidal capnography, in addition to

pulse oximetry, will facilitate early detection of ventilatory insufficiency and allow supportive interventions before adverse consequences occur.

4. *History of asthma, currently wheezing, acute URI*: If the patient's wheezing clears readily with a single albuterol nebulization treatment, the increased risk of sedation-related adverse respiratory events likely is low, but providers should be prepared to administer additional asthma care if needed. The acute URI may increase the risk of laryngospasm, especially if the patient is febrile. It is unclear whether administration of a drying agent such as glycopyrrolate or atropine reduces this risk.

PSA Technique Options

(a) *Ketamine with or without Midazolam*: If vascular access is successful, the intravenous route is preferred as it allows titration to effect and use of the smallest effective dose, with repeat small doses as needed, thus decreasing length of recovery. Please see Case 1 for further information on ketamine dosing. It is likely this patient will need multiple subsequent painful burn debridements. Therefore, effective analgesia and amnesia for this initial burn care are especially important to establish the patient's future expectations. A sedating dose of midazolam, 0.1 mg/kg, prior to ketamine infusion, may increase the probability of complete procedural amnesia. A potential additional benefit for this patient is ketamine-induced reduction of central sensitization and windup from continued burn pain. While the risk of laryngospasm associated with ketamine is quite low, the presence of an active URI may increase this risk and the sedation providers should be prepared to manage this potentially life-threatening adverse event.

Intramuscular ketamine 4 mg/kg: Please see Case 1 for additional information.

(b) *Fentanyl + Midazolam or Propofol*: provides effective PSA but requires vascular access. Please see Case 2 for additional information.

(c) *Nitrous oxide 50–70%* is unlikely to provide sufficient PSA for vigorous burn debridement in this young child unless it is coadministered with a potent systemic analgesic such as fentanyl or ketamine. These combinations can readily induce deep sedation and general anesthesia and should be considered only by providers experienced in such techniques.

Case 4

A 2 year-old boy has a *complex forehead laceration* that requires suturing. Topical anesthetic gel was applied in triage. Despite best efforts to calm him as he sits in his mother's lap, he continues to cry and vigorously resists exam. His mother predicts he will not calm and indicates this is typical behavior during interactions with healthcare providers.

Issues: The laceration repair requires the patient's forehead to be still, physical restraint will likely reinforce similar behavior during future health care; there are other ED patients waiting more than 4 h to be seen.

PSA Options

(a) *Nitrous oxide 50–70%* provides effective calming for laceration repair in young children. A continuous circuit or other N_2O delivery system with a standard mask that covers the patient's mouth and nose and is designed for use by children is necessary for effective PSA with N_2O. Dental type nose masks are less effective since they allow mouth breathing that bypasses the N_2O. If the laceration is on the chin or in an area covered by the standard mask, a neonatal size mask may be used as a nose-mask and the child's mouth gently

held closed. If the mother is amenable, this technique can be enhanced by administering the N_2O and suturing as the child sits in her lap with his head rested on her chest and her singing favorite songs or telling stories for distraction. A helper will need to help steady the child's head and gently hold the mask in place over the patient's mouth and nose. All must be vigilant for vomiting, often forewarned by abdominal or chest heaving. The N_2O should be administered for about 2 min before attempting to provide additional anesthesia (buffered lidocaine injected with a half-inch 30 gauge needle recommended) or suturing.

(b) *Midazolam intranasally* 0.2–0.4 mg/kg administered with atomizer to spray small volumes of concentrated intravenous solution (5 mg/mL) to improve absorption. Suggested dose for this 12 kg child is 5 mg or 1 mL. Divide the 1 mL total dose into four sprays of ~0.25 mL; alternate nostrils, allow about a minute between repeat sprays into a given nostril. Use of small volumes improves efficacy by reducing drainage of drug into posterior pharynx from which it is less well absorbed and causes an unpleasant taste. Onset of sedation occurs by 3–5 min with duration of 20–40 min. As with other routes of midazolam administration, some children become dysphoric instead of sedated. When administered with an atomizer, intranasal midazolam is well tolerated and achieves anxiolysis with mild sedation. If the intravenous solution is dripped into the nares without atomization, most children complain of a burning sensation.

(c) *Ketamine intramuscularly* 2–3 mg/kg provides effective PSA for suturing when local anesthesia is also used. Minor restraint may be needed in a few children with this dose. Onset of sedation usually occurs by 5 min and recovery by 60–80 min.

(d) *Propofol, Ketamine, or Fentanyl/Midazolam intravenously*: titration of any of these techniques will provide maximum effectiveness but intravenous access is required. Placement of an IV catheter in this resistant child certainly will require physical restraint unless it is inserted after sedation with N_2O, intranasal midazolam, or IM ketamine. Such strategy might be logical for a very complex laceration repair expected to last more than 20–30 min or involve a critical step that requires the patient to be motionless, such as approximating a lacerated eyelid margin.

Case 5

An otherwise healthy febrile 10-month-old infant needs *incision and drainage of a large buttock abscess*.

PSA Options

1. Ketamine IV or IM: see Case 2 for additional information.
2. Fentanyl + Propofol or Midazolam: see Case 2 for additional information.
3. Nitrous oxide + Oxycodone can provide acceptable PSA if effective local anesthesia of the abscess can be achieved. Field blocks with buffered lidocaine are variably effective for smaller abscesses but usually unsuccessful for large abscesses. For larger and deeper abscesses, the author has occasional success by partially draining the abscess through a small (~1 cm) incision through skin well-anesthetized with subcutaneous lidocaine. The abscess cavity then is gently refilled with the topical anesthetic solution commonly used for anesthetizing lacerations (4% Lidocaine, 1:100,000 Epinephrine, and 0.5% Tetracaine (L.E.T.)). After 30 min, the entire abscess cavity often is well-anesthetized and the patient tolerates widening the incision and debridement of the cavity under N_2O sedation.

Case 6

You are asked to provide sedation for *incision and drainage of a peri-tonsillar abscess* in a very anxious 5-year-old boy who vigorously resists oropharyngeal exams. He has had a runny nose and cough with low grade fever for 2–3 days.

Issues: Mild to light moderate PSA can safely be administered for I&D of peritonsillar abscesses in older children and teens who will cooperate with the procedure in the Emergency Department. However, this child will require deep sedation to overcome his resistance. Deep sedation by any technique carries increased risk of pulmonary aspiration due to variable blunting of protective airway reflexes. This patient will have blood and pus draining upon his larynx during the procedure. This patient should be considered for abscess drainage in the O.R. under general anesthesia, likely with endotracheal intubation.

For light PSA for peritonsilar abscess I&D in cooperative children, 30–45 min prior to the procedure we administer morphine for baseline pain management and glycopyrrolate to dry secretions. Five to ten minutes prior to the procedure, we administer 2 mg of midazolam for anxiolysis. If the patient has difficulty tolerating the mucosal injection of buffered lidocaine with epinephrine at the site of the abscess, we may infuse 0.1–0.2 mg/kg of ketamine immediately prior to the surgeon's incision, i.e., a small dose. The patient is able to follow commands but appears a bit dazed after the ketamine and usually is better able to tolerate the procedural pain. Laryngospasm has been found to occur more frequently during endoscopy with ketamine sedation, presumably due to direct stimulation of the larynx. Whether laryngospasm risk correlates directly with the dose of ketamine is unclear. Likewise, it is unclear whether risk of laryngospasm is increased with laryngeal stimulation by drainage from a peritonsilar abscess. Using this approach, none of our patients have developed laryngospasm during peritonsilar I&D in our ED.

Case 7

A 15-month-old boy has fallen through stair railings an hour ago and has a large hematoma on his left parietal area. He is irritable and restless. An emergent head CT scan to evaluate for intracranial injury has been ordered. The CT tech calls to state they cannot get the patient to lay still for the brief period of the scan and asks that the patient be sedated.

Issues: Need for emergent CT scan that requires motionless patient for about 1 min to conduct scan, potentially increased intracranial pressure from hemorrhage.

PSA Options

1. Pentobarbital intravenously will sedate patient but a full dose may cause mild reduction in blood pressure which impacts brain perfusion. The prolonged recovery from pentobarbital makes monitoring patient for neurologic deterioration difficult and may complicate plans for general anesthesia if emergent craniotomy is needed.
2. Ketamine intravenously 0.25–0.5 mg/kg, pushed rapidly, will provide brief sedation. Some restraint may be necessary. Blood pressure likely will be maintained and brief increase in intracranial pressure probably is not critical.
3. Propofol intravenously provides sedation but brief hypotension and respiratory depression may rapidly worsen patient condition.
4. Etomidate intravenously will provide sedation and recovery within 5–10 min with less risk of hypotension. Myoclonic jerks during induction of sedation tend to be brief but may interfere with scanning.
5. Midazolam intravenously may be insufficient for sedation.
6. Fentanyl intravenously for pain may be sufficient to coax patient to be still for the brief period, as needed.

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