Sedation in the Intensive Care Unit: Challenges, Outcomes, and Future Strategies

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Introduction

On a daily basis, infants and children in the Pediatric Intensive Care Unit (PICU) require sedation and analgesia during painful and invasive procedures. Regardless of the patient's age, underlying medical condition or comorbidities, admission to and subsequent care in the PICU can be a frightening and painful experience. As in other locations, procedures may be brief (burn dressing changes, placement of central venous or arterial cannulae), and require only a short period of analgesia, anxiolysis, or immobility. However, the PICU is often different from other locations, as the need for procedural sedation may last days or even weeks as children may require prolonged sedation to overcome the pain and anxiety associated with the presence of an endotracheal tube (ETT) and the requirement for ongoing mechanical ventilation. The pain and anxiety may be further magnified by various psychological factors including periodic separation from parents, disruption of the day–night cycle, unfamiliar people, the noise of imposing machines and monitoring devices, fear of death, and loss of self-control can lead to emotional distress, anxiety, and sleeplessness. In a recent prospective cohort study of adult patients, Mendelsohn et al. reported that 26.3% of their cohort remembered mechanical ventilation and approximately 25% would have chosen not to receive mechanical ventilation had it been any more painful [1].

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Pediatric ICU Sedation

Preprocedure Preparation and Patient Evaluation

Before the administration of pharmacologic agents for the control of procedure-related pain and anxiety, there should be an evaluation of the patient and preparation of the environment (Table 13.1). The Pediatric ICU patient is somewhat different in that treatable and potentially life-threatening causes of agitation such as hypoxemia, hypercarbia, cerebral hypoperfusion, necrotic bowel, or a compartment syndrome must be excluded before instituting sedation or escalating doses. The injudicious use of sedative/analgesic agents without ongoing patient examination and monitoring may be deleterious. Alternatively, such concerns are less of an issue for a patient who is undergoing a brief invasive or noninvasive procedure.

The basic components of the presedation assessment are outlined in Table 13.2. This assessment includes the performance of a focused history and physical examination. The history

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Table 13.1 Preparation for procedural sedation in the pediatric ICU

Rule out treatable causes of agitation
Hypoxia and hypercarbia
Cerebral hypoperfusion
Bladder distention
Surgical lesion – necrotic bowel or compartment syndrome
Perform a presedation evaluation of the patient. This evaluation is similar to that performed prior to any surgical procedure performed in the operating room
Identify the etiology of the pain or agitation to guide the appropriate selection of the agent or agents as well as the need to provide sedation/anxiolysis/amnesia, analgesia or both
Monitor patient according to the standards outlined by the American Academy of Pediatrics for procedural sedation and analgesia [2]
Titrate the initial bolus dose of the medication and subsequent infusion rates based on the patient's clinical response with the use of formalized sedation/pain scales
Observe for adverse physiologic effects including the development of physical tolerance which necessitates increasing the dose of the agent used or switching to another agent that acts through a different receptor system

Table 13.2 The preprocedure or presedation assessment

Patient's name, age weight, and gender
Past medical history
Acute medical or surgical problems
Comorbid medical conditions
Previous sedation or anesthetic history including problems
Allergies
Current medications
Family history of anesthetic complications
Dietary history (nil per os status)
Pregnancy history
Physical examination
Baseline vital signs including room air oxygen saturation if feasible
Airway examination with Mallampati grading system
Focused cardiac and respiratory examination
Current vascular access and infusion (to select site for medication administration)
Laboratory evaluation as appropriate
Summary
American Society of Anesthesiologists status (ASA I–V)
Sedation and recovery plan
Risks discussed and informed consent obtained from patients

should focus on the child's current state of health as it relates to the reason for the procedure, the past medical history to identify significant comorbidities, as well as acute events which led to the PICU admission. Since the primary risks associated with sedation include adverse respiratory events (apnea, hypoxemia, hypercarbia, and upper airway obstruction) or cardiovascular events (hypotension, bradycardia, arrhythmias), the focus of the presedation evaluation and physical examination is placed on these systems or areas. Although many patients may already have an ETT in place, the assessment of the upper airway should still be performed in the event that the ETT become dislodged at some time such as during positioning for the procedure or patient transport. Upon completion of the history and physical examination, an ASA (American Association of Anesthesiologist) classification may be assigned and the various options for sedation regimens considered (Table 13.3) [2].

A final component of the presedation assessment is the establishment of when the child last had any oral intake (nil per os or NPO status). Recently, the need to adhere to strict NPO guidelines for procedural sedation has been challenged, particularly by those working in acute-care environments such as emergency rooms where procedures may need to be performed more urgently [3–6]. In specific cases in the Pediatric ICU patient, such as patients who have recently eaten, those with comorbid conditions which affect gastric emptying, those with altered mental status or impaired airway protective reflexes, and those with preexisting problems with respiratory or cardiovascular function, the safest way to proceed may include a rapid sequence induction and endotracheal intubation to provide airway protection during the procedure.

Given that any of the agents used for procedural sedation and analgesia can have deleterious effects on physiologic functions, patients should be monitored in accordance with guidelines set forth by the American Academy of Pediatrics (AAP) and/or the ASA during and following the use of these agents [3, 7, 8]. Although the PICU provides the optimal environment for the monitoring of a patient's physiologic functions, this monitoring should be continued when patients are transported out of the PICU [3, 7].

Table 13.3 Suggested guidelines for dosing of sedative and analgesic agents[a]

Agent	Dose	Comments
Fentanyl	2–3 μg/kg/h	Modulates the postsurgical and sympathetic stress response thereby blunting increases in pulmonary vascular resistance (PVR). May have utility in neonates and infants at risk for pulmonary hypertension following surgery for congenital heart disease. Has limited effects on cardiac output and mean arterial pressure. May result in mild to moderate negative chronotropic effects
Morphine	10–30 μg/kg/h	Cost-effective agent for sedation. Hemodynamic effects are generally related to vasodilation of capacitance vessels and a decrease in preload. These effects are exaggerated in the setting of hypovolemia. Delayed development of tolerance and less withdrawal issues when compared to fentanyl
Remifentanil	0.1–0.3 μg/kg/min	Short (4–8 min) and consistent half-life across all age groups including neonates and infants due to esterase metabolism. Use for prolonged (more than 24 h) sedation limited by the rapid development of tolerance and cost
Midazolam	0.05–0.15 μg/kg/h	Abundant clinical experience as an agent for PICU sedation. Metabolism by the P_{450} may result in prolonged half-life in patients with hepatic dysfunction. Presence of an active metabolite may result in prolonged sedation with long-term administration. Generic form limits cost when compared with other agents
Lorazepam	0.025–0.05 μg/kg/h	Limited clinical experience as an agent for sedation in the PICU population. Generic preparations limit cost. A major consideration is the accumulation of its diluent, propylene glycol. Metabolism by glucuronyl transferase limits changes in pharmacokinetics even with hepatic dysfunction
Ketamine	1–2 μg/kg/h	Endogenous catecholamine release results in bronchodilation and cardiovascular stability. However, may cause cardiovascular collapse in patients whose endogenous catecholamines are depleted as its primary direct effects are a decrease in myocardial function. Controversial effects on intracranial pressure (IP) and PVR although the recent literature demonstrates no deleterious effects
Pentobarbital	1–2 μg/kg/h	Second line agent after benzodiazepines and opioids. Alkaline pH leads to compatibility issues with other medications and may result in tissue irritation or sloughing of skin with extravasation. Hypotension may occur from vasodilatation and negative inotropic effects
Propofol	1–3 μg/kg/h	Rapid awakening upon discontinuation of the infusion. Solution has a high lipid content. Prolonged use (≥12 h) for sedation contraindicated in the PICU population due to risk of propofol infusion syndrome. Increasing data suggests that this may also occur in the adult population. May still be used in rare circumstances as a therapeutic agent for the treatment of increased ICP or status epilepticus; however, intermittent monitoring of acid–base status is suggested to monitor for toxicity
Haloperidol	0.06–0.45 μg/kg/day	Limited clinical experience in the pediatric population. Anecdotal data in the adult population suggest benefits of a decreased incidence of withdrawal and delirium with its use. May have a role for the treatment of agitation and delirium in the PICU population. Hypotension may result from α-adrenergic blockade. Additional adverse effects include lowering of the seizure threshold and the potential for cardiac arrhythmias due to prolongation of the QT interval
Dexmedetomidine	0.25–1 μg/kg/h	FDA approved for short-term (24 h) sedation in adults. Increasing experience in the pediatric population. Mechanism of action may limit delirium in the adult ICU setting. Adverse effects on hemodynamic function include bradycardia and hypotension

[a]The listed infusion rates are suggestions for starting doses. The actual infusion rate should be titrated up or down based on the patient's actual requirements and the response to the agent

Assessing the Depth of Sedation

During the use of sedative and analgesic agents, the repeated evaluation of the depth of sedation should be incorporated into the PICU routine with an increase or decrease in the doses used based on the patient's response. Clinical practice has included the move from the use of subjective measures and assessments made by healthcare providers to the use of formal pain and sedation scoring systems, which are monitored at regular intervals with the recording of physiologic vital signs.

These scoring systems include both those used during prolonged sedation during mechanical ventilation as well as those used for brief periods of time during procedural sedation.

The currently used PICU sedation scores evaluate either physiologic variables, an objective assessment of the patient's depth of sedation, or a combination of the two. One commonly used scale, the COMFORT score, combines the scoring of a patient's response or movement in addition to various physiologic parameters [11]. It relies on the measurement of alertness, respiration, blood pressure, muscle tone, agitation, movement, heart rate, and facial tension. This scoring system has been validated in the pediatric-aged patient and may have utility in the assessment of sedation during mechanical ventilation [11, 12]. However, scales that use physiologic parameters can be misleading in an ICU setting where alterations in vital signs can occur unrelated to the level of sedation. Furthermore, patients with cardiovascular dysfunction requiring vasoactive medications may not manifest increases in heart rate and blood pressure even in the presence of severe agitation or pain.

Ista et al. have recently proposed a modification of the original COMFORT score known as the COMFORT-B score which eliminates the use of physiologic variables and provides new cutoff points for the diagnosis of oversedation or undersedation [13]. Other scoring systems such as the Sedation-Agitation Scale (SAS) also eliminate the use of physiologic parameters. The SAS visually assesses the level of the patient's comfort and grades it from 1 (unarousable) to 7 (dangerous agitation such as pulling at the ETT) [14]. The Ramsay Scale, a sedation scale used commonly in the adult ICU population, also assigns a value based on the observation of the patient, but also uses a tactile stimulus (a glabellar tap) to distinguish between the deeper levels of sedation [15]. Scoring for the Ramsay Scale varies from 1 (awake, anxious, and agitated) to 6 (no response to a glabellar tap). The Hartwig score similarly uses a visual assessment of the patient, but as with the Ramsay Scale includes a response to a noxious stimulus, in this case, tracheal suctioning thereby eliminating its use in nonintubated patients [16]. Scales such as the Ramsay and the Hartwig that assess the response to a tactile stimulus require disturbing the patient to differentiate between the deeper levels of sedation. Additionally, scales that evaluate a patient's response to a stimulus or observe their behavior are not valid during the administration of neuromuscular blocking agents which prevent movement.

Various other scales have also been developed for assessing the patient during procedural sedation. The Observers Assessment of Alertness/Sedation (OAAS) scale has been validated in children, but has been shown to have a limited ability to differentiate between the deeper levels of sedation [17]. The Vancouver Sedative Recovery Scale appears to be better able to differentiate deeper levels of sedation, although it is likely too cumbersome to be easily utilized during short procedures [18]. More recently, Malviya et al. developed and validated the University of Michigan Sedation Scale (UMSS) [19]. This scale was developed to be a simple and efficient tool to assess depth of sedation over the entire sedation continuum and one that could easily be applied by various healthcare providers. It utilizes a simple scale ranging from 0 (awake and alert) to 4 (unresponsive).

However, none of these sedation scales meet all of the needs of the PICU provider. As such, there remains an interest in the use of monitoring technology to assess the depth of sedation through the analysis of the electroencephalogram (EEG). The bispectral index (BIS monitor) (Aspect Medical, Newton, MA) uses a programmed algorithm to evaluate the processed EEG pattern and provide a numeric value ranging from 0 (isoelectric) to 100 (awake with eyes open). Its predominant clinical use has been to monitor the effects of general anesthesia.

Although still somewhat controversial, it has been suggested that maintenance of a BIS value less than 60–70 correlates with a low probability of intraoperative awareness [20, 21]. The BIS monitor has been used in settings outside of the operating room for assessment during procedural sedation or mechanical ventilation [22–30]. Gill et al. compared BIS values with Ramsay sedation

scores in 37 adults who received procedural sedation in the emergency room setting [22]. There was a wide variability in BIS values at similar sedation scores. The BIS was most effective at differentiating moderate-to-deep sedation from general anesthesia.

Brown McDermott et al. compared BIS values with UMSS scores during procedural sedation administration in 86 children less than 12 years of age [23]. Although there was a good correlation between the BIS value and the sedation score, a wide variability in the range of BIS values for each level of sedation was again noted. The BIS monitor was ineffective at determining the depth of sedation with ketamine or a combination of oral chloral hydrate, hydroxyzine and meperidine.

Despite these shortcomings, the BIS monitor may be able to effectively identify patients who are becoming too deeply sedated and may therefore be at risk for adverse respiratory events. Motas et al. demonstrated that the depth of sedation as judged by the BIS monitor was predictive of adverse airway events during the administration of procedural sedation (either propofol, midazolam or pentobarbital) by nonanesthesiologists [24].

BIS monitoring has also been evaluated as a means of evaluating the depth of sedation during prolonged mechanical ventilation. Although the results have been somewhat mixed, the majority of reports have demonstrated a clinically acceptable correlation between the BIS monitor and commonly used ICU sedation scores including the Ramsay or the COMFORT score [25–31].

The more recent versions of the BIS probe incorporate a sensor to reduce electromyographic (EMG) interference. The BIS algorithm was developed for use with propofol or the potent inhalational anesthetic agents which work through the γ-amino butyric acid (GABA) system. Therefore, the BIS monitor is not accurate with the administration of etomidate or agents which act through the *N*-methyl-d-aspartate (NMDA) system including xenon or nitrous oxide [32–34]

Despite these issues, our clinical experience suggests that some form of depth of sedation monitoring may be particularly efficacious in situations that preclude the use of conventional ICU scoring systems (patients receiving neuromuscular blocking agents and/or medications that may alter heart rate and blood pressure responses) [35–38]. The BIS monitor provides a continuous numeric readout using a simple 0–100 scale that is immediately available at the bedside as opposed to sedation scoring systems that provide only an intermittent assessment and require time to assess and tabulate the various parameters

Basic Principles

Several variables should be considered when providing therapeutic sedation and analgesia for the PICU patient. Unfortunately, there is limited evidence-based medicine from which to develop guidelines for the use of sedative and analgesic agents in the PICU setting (Table 13.3). There are still limited studies which evaluate the pharmacokinetics and pharmacodynamic properties of analgesic and sedative drugs in critically ill infants and children [39–41]. Pharmacokinetic studies are generally performed in healthy adult volunteers with the extrapolation of these results to infants and children. The comorbidities present in the PICU may affect several variables including volume of distribution and elimination half-life thereby further altering the pharmacokinetics or these agents. Additional variabilities in the PICU setting are likely to result from drug–drug interactions, end-organ (hepatic, renal) failure or dysfunction, malnutrition, low plasma proteins with altered drug binding, alterations in uptake of the medication if nonintravenous routes are used, and alterations in drug distribution. Pharmacogenetic factors may also affect responses to medications as we are beginning to learn that there are genetic differences that affect the way we respond to acute illness and the way we metabolize various medications [42, 43].

An example of such variability in the PICU population is demonstrated by an evaluation of fentanyl infusion requirements during mechanical ventilation in neonates and infants [44]. The fentanyl infusion requirements varied from 0.47 up to 10.3 μg/kg/h to achieve a similar effect. Therefore, it is not feasible to approach the provision of sedation and analgesia in the PICU patient using a "cookbook." The dosing recommendations provided in this chapter for the specific medications discussed are meant only as guidelines for starting doses which may be titrated to effect [45].

Despite the potential difficulties and risks of sedation and analgesia in the PICU patient, there may be significant benefits. Aside from humanitarian concerns, clinical trials have reported decreases in morbidity and mortality based on the analgesic regimen following cardiovascular surgery for congenital heart disease in neonates and infants [46, 47]. These effects are postulated to be the result of blunting of the endogenous physiologic stress response thereby decreasing release of endogenous catecholamines and adrenal cortical hormones. This physiologic stress response, when excessive, may have deleterious end-organ effects. Analgesia and sedation may facilitate cardiac and respiratory support such as permissive hypercapnia, reverse I:E ratio ventilation, high-frequency ventilation, and extracorporeal support. It may also provide therapeutic benefits in the treatment of intracranial hypertension or to modulate pulmonary vascular resistance (PVR) in patients at risk for pulmonary hypertension and limit the need for neuromuscular blocking agents and their associated adverse effects [48].

Choice of Agent and Route of Delivery

The three primary decision points for sedation and analgesia in the PICU include the agent, its route of administration, and its mode of administration. As no agent will be effective in every patient or scenario, basic knowledge regarding the various agents allows the healthcare provider to switch from one agent to another when the first line drug is either ineffective or associated with adverse effects. In the remainder of this chapter, a brief discussion of each agent is provided and its use in the PICU setting discussed.

Although the intravenous route is chosen in most clinical scenarios, alternative routes may be required in specific clinical scenarios or patient populations. Furthermore, there is expanding knowledge and interest regarding the use of alternative routes especially inhalational anesthesia or subcutaneous administration in the PICU setting. This chapter will review the clinical experience and the pertinent literature associated with the common sedatives and analgesics in the PICU.

Inhalational anesthetic agents

The potent inhalational anesthetic agents are used on a daily basis during the perioperative period to provide amnesia and analgesia during major surgical procedures. Based on their chemical structure, these agents can be divided into alkanes such as halothane or substituted ethers. The substituted ethers include either methyl, ethyl ethers such as isoflurane, desflurane, and enflurane or methyl, isopropyl ethers such as sevoflurane. The characteristics of these agents which may make them useful agents for ICU sedation include a rapid onset, rapid awakening upon discontinuation, and the ability to rapidly control the depth of sedation. The potent inhalational anesthetic agents also provide specific therapeutic end-organ effects including bronchodilatation, myocardial preconditioning, and cerebral protection. Although experience with use of the potent inhalational anesthetic agents for ICU sedation in the United States is limited, certain centers in Europe and the United Kingdom have reported favorable experiences with these agents in adult ICU patients [49–52]. Despite the fact that these agents are all considered in the category of the potent inhalational anesthetic agents, their physiologic effects are distinctly different.

Various adverse physiologic effects have been reported with halothane including a negative inotropic and chronotropic effect on myocardial function, the potential for a proarrhythmogenic effect especially in the setting of increased catecholamines or when used in conjunction with

other medications (e.g., aminophylline), and the potential for the development of hepatitis related to an immunologic reaction directed against the oxidative metabolite, trifluoroacetic acid [53, 54]. Although hepatitis may occur with the other inhalational anesthetic agents including isoflurane, its incidence is less with isoflurane due to its limited metabolism of 0.2% compared with that of halothane (15–20%).

Given the potential for adverse effects on myocardial function and its association with perioperative cardiac arrests in infants and children, halothane is no longer in use in the United States. Likewise, given its adverse effect profile and the introduction of newer agents, enflurane is disappearing from anesthetic practice throughout the world. Adverse effects with the prolonged administration of enflurane include negative inotropism and the release of fluoride during metabolism. Plasma fluoride concentrations in excess of 50 μmol/L can have deleterious effects on renal function with a decreased glomerular filtration rate and renal tubular resistance to vasopressin with nephrogenic diabetes insipidus. Three to five percent of sevoflurane also undergoes metabolism and like enflurane, sevoflurane is highly substituted with fluoride. Therefore, its prolonged administration can also result in elevated serum fluoride concentrations.

Desflurane is the newest of the inhalational anesthetic agents. Its beneficial properties include low blood:gas and blood:fat solubility coefficients thereby resulting in a rapid onset and rapid awakening upon its discontinuation. When compared with propofol for postoperative sedation of adults requiring mechanical ventilation, there was a shorter and more predictable emergence time and a faster return of mental recovery with desflurane compared to propofol with no difference in the incidence of adverse effects [51]. Drug costs were lower with desflurane than with propofol (95€ for desflurane vs. 171€ for propofol per 24 h) with additional costs of soda lime (5€) being comparable to the costs of infusion tubing for propofol (2.5€). Adverse effects with desflurane include hypotension primarily from peripheral vasodilatation, rebound tachycardia from stimulation of the sympathetic nervous system which occurs primarily with rapid increases in the inhaled concentration or the use of inspired concentrations in excess of 6% (a concentration not likely to be required in the ICU setting), direct irritant effects on the airway thereby making it less than optimal in patients with airway hyperreactivity, and rare reports of carbon monoxide formation due to desflurane's interaction with dessicated soda lime.

Additional concerns with all of the inhalational anesthetic agents include their potential as a trigger agent for malignant hyperthermia, cost issues, effects on intracranial pressure (ICP), and alterations of the metabolism of other medications. As nonspecific vasodilators, all of the inhalational anesthetic agents cause cerebral vasodilatation resulting in an increase in ICP in patients with compromised intracranial compliance. Cerebral vasodilatation can be partially blunted by hyperventilation to a $PaCO_2$ of 25–30 mmHg [55, 56]. The inhalational anesthetic agents alter the metabolism of several mediations which may be used in the PICU setting including lidocaine and other local anesthetic agents, β-adrenergic antagonists, and benzodiazepines [57].

To date, there is a limited experience with the use of the potent inhalational anesthetic agents for sedation in the PICU setting. Arnold et al. reported their experience with isoflurane for sedation in ten pediatric patients (3 weeks to 19 years), who required endotracheal intubation and mechanical ventilation [58]. The duration of isoflurane administration ranged from 29 to 769 h (245 ± 225 h). Sedation was initiated with isoflurane at an inspired concentration of 0.5% and adjusted in 0.2% increments as needed. There was adequate sedation 75% of the time, excessive sedation 4% of the time, and inadequate sedation 21% of the time. In the five patients who received isoflurane for at least 96 MAC (minimum alveolar concentration)-hours, there were no differences in blood urea nitrogen, serum creatinine, osmolality, bilirubin, and alanine aminotransferase between time 0 and 96 h. The duration of isoflurane administration correlated directly with the plasma fluoride concentration. Five of the patients, who had received greater than 70 MAC-hours, manifested

signs and symptoms suggestive of withdrawal including agitation and nonpurposeful movements when the isoflurane was discontinued.

Despite the potential advantages of using the potent inhalational anesthetic agents for sedation in the ICU setting, logistic problems regarding delivery of these agents may limit applicability in the ICU setting [50].

Given the problems with the devices and techniques currently available for the delivery of the potent inhalational anesthetic agents in the ICU setting, novel means of delivering these agents are needed. The Anesthetic Conserving Device or "AnaConDa®" (ACD, Hudson RCI, Upllands Väsby, Sweden) is a modified heat-moisture exchanger which may allow a simplified means of administering the inhalational anesthetic agents in the ICU setting. The device is placed between the Y-piece of the ventilator circuit and the ETT. There is also a port at the end of the device just proximal to its attachment to the ETT which allows gas sampling and monitoring of the agent concentration. The desired inspired concentration is titrated by adjusting the infusion rate on the syringe pump based on the manufacturer's recommendations. Exhaled isoflurane is adsorbed to the lipophilic carbon particle filter in the device and redelivered to the patient thereby limiting environmental pollution.

Sackey et al. evaluated the ACD in the ICU setting in 40 adult patients requiring sedation for more than 12 h [59]. The patients were randomized to sedation with isoflurane administered with the ACD or a continuous infusion of midazolam. The inspired isoflurane concentration was started at 0.5% (infusion rate on the syringe pump of 1–3.5 mL/h according to the manufacturer's recommendations) while midazolam was infused at 0.02–0.05 mg/kg/h. The infusion rates were adjusted as needed and opioids administered for analgesia. The percentage of time within the desired level of sedation was similar between the two groups (54% with isoflurane and 59% with midazolam) with no difference in opioid requirements or the need for bolus doses of sedative agents. The time to extubation (10 ± 5 vs. 252 ± 271 min) and the time to follow verbal commands (10 ± 8 vs. 110 ± 132 min) were shorter with isoflurane than with midazolam. Anecdotal experience with the device has also been reported in three pediatric patients who required sedation during mechanical ventilation or in the treatment of status epilepticus [60].

Benzodiazepines

The benzodiazepines remain the most commonly used agent for sedation during mechanical ventilation in the PICU patient. These agents produce amnesia, anxiolysis, and sedation through their effects on the inhibitory neurotransmitter, GABA. Benzodiazepines bind to the α-subunit of the GABA receptor thereby facilitating binding of the GABA molecule to the β-subunit. This interaction increases chloride conduction across the neuronal membrane resulting in hyperpolarization. Benzodiazepines in common clinical use in the United States for sedation in the PICU include midazolam and lorazepam. Diazepam was formerly a commonly used agent for sedation in both pediatric and adult ICUs. Its high lipid solubility results in a rapid onset of action; however, its low water solubility requires administration in a solution of propylene glycol which can cause pain and thrombophlebitis when administered through a peripheral vein. Diazepam is also available in a lipid formulation which has been shown to alleviate the discomfort associated with the intravenous administration of the propylene glycol preparation [61, 62]. Diazepam has fallen out of favor as an agent for sedation in the PICU setting because of its prolonged duration of action as well as its metabolism to active compounds with elimination half-lives that far exceed the parent compound. With repeated administration, the metabolites can accumulate and result in prolonged sedation and delayed awakening once the drug is discontinued.

Midazolam is an imidazobenzodiazepine with a rapid onset of action and a short elimination half-life [63]. Clinical experience and years of its use have demonstrated the efficacy of continuous midazolam infusions for sedation in the PICU patient in doses ranging from 0.05 to 0.2 mg/kg/h [64–66]. Its availability in generic form makes it a cost-effective form of sedation.

Rosen and Rosen retrospectively reviewed their experience with midazolam infusions for

sedation during mechanical ventilation in 55 pediatric patients [66]. Midazolam dosing was initiated with a bolus dose of 0.25 mg/kg followed by a continuous infusion of 0.4–4 μg/kg/min (0.02–0.2 mg/kg/h). Midazolam was effective in all patients without significant hemodynamic effects. The authors noted that midazolam became ineffective in one patient following the institution of ECMO and related this to midazolam binding to the surface of the membrane oxygenator. Similar efficacy has been reported by other investigators [67].

Although intravenous administration is generally the route chosen in the PICU patient, midazolam remains unique among many of the other agents used for sedation in the ICU setting in that alternative, nonintravenous routes of delivery have been used clinically including oral, rectal, transmucosal (nasal, rectal, sublingual), and subcutaneous administration [68–72]. With all of these nonintravenous routes except for subcutaneous administration, increased doses are required due to decreased bioavailability.

In many centers in the United States, oral midazolam is currently the preferred agent for premedication in the operating room. Doses for oral administration have ranged from 0.25 up to 0.7 mg/kg. The primary disadvantage of oral administration is that the IV preparation (5 mg/mL) is generally used which contains the preservative, benzyl alcohol, thereby giving the drug a very bitter taste.

A commercially available preparation of midazolam in a cherry-flavored solution for oral administration is available (Versed syrup, Roche Laboratories Inc, Nutley, NJ). Because of the control of pH during the manufacturing process, clinical data suggest that effective sedation can be achieved with doses as low as 0.25 mg/kg compared to the 0.5–1.0 mg/kg doses reported when using the IV preparation diluted in other solutions for oral administration [73]. Additional nonparenteral administration routes include intranasal and sublingual administration. The dose (0.2–0.4 mg/kg) is lower and the onset more rapid when compared to the oral route as midazolam is rapidly absorbed across both mucosal surfaces with sedation occurring in as little as 5–10 min. With intranasal administration, the preservative, benzyl alcohol, may burn the nasal mucosa. This is avoided with sublingual administration, but issues of taste and patient cooperation may limit the usefulness of this route.

Midazolam is metabolized by isoforms of the hepatic P_{450}3A enzyme system to the major hydroxylated metabolite, 1-OH midazolam. 1-OH midazolam is approximately equipotent with the parent compound. It undergoes further hepatic metabolism via the glucuronyl transferase system to 1-OH midazolam-glucuronide, a water soluble metabolite, which is renally excreted. In the presence of renal insufficiency, 1-OH midazolam-glucuronide accumulates thereby potentiating the effects of midazolam [74]. Several factors including age and underlying illness may also alter midazolam pharmacokinetics. With metabolism dependent on the hepatic P_{450} system, clearance changes from infancy to adult age and with alterations in hepatic function [75, 76]. Additional changes may occur related to critical illness. In a cohort of 21 PICU patients, midazolam clearance was significantly longer (5.5 ± 3.5 h) than that reported in healthy age-matched children (1.2 ± 0.3 h) [77, 78].

Lorazepam is a water soluble benzodiazepine that is metabolized by glucuronyl transferase. Its metabolites are pharmacologically inactive. Medications known to alter the P_{450} system (anticonvulsants, rifampin, cimetidine) do not alter lorazepam's pharmacokinetics. In advanced liver disease, phase II reactions (glucuronyl transferase) are better preserved than phase I reactions (P_{450} system) so that the pharmacokinetics of lorazepam remains unchanged. The Society of Critical Care Medicine guidelines for sedation of adult patients in the ICU setting has recommended lorazepam as the preferred sedative [79].

In comparison to midazolam, there are fewer reports regarding the use of lorazepam for sedation in both the pediatric and the adult ICU population [80, 81]. When comparing lorazepam with midazolam in adult ICU patients, the mean infusion rates to achieve adequate sedation were 0.06 mg/kg/h for lorazepam and 0.15 mg/kg/h for midazolam [80]. There were fewer infusion

rate adjustments per day with lorazepam than with midazolam (1.9 for lorazepam vs. 3.6 for midazolam). The mean time to return to baseline mental status was shorter with lorazepam (261 min with lorazepam vs. 1,815 min with midazolam).

Lugo et al. suggested the use of enteral lorazepam to decrease intravenous midazolam dosing requirements and drug costs during mechanical ventilation in a cohort of 30 infants and children [82]. Midazolam was used for sedation until the requirements were stable for 24 h. Enteral lorazepam was dosed at 1/6th of the total daily intravenous midazolam dose. There was a significant reduction in midazolam requirements on day 1 and by day 3, the midazolam infusion was discontinued in 24 of 30 patients. Enteral lorazepam has also been successfully used for the treatment or prevention of withdrawal following the prolonged administration of intravenous benzodiazepines for sedation during mechanical ventilation in the PICU population [83].

Each milliliter of the intravenous lorazepam solution (2 mg lorazepam per mL of solution) contains 0.8 mL or 800 mg of propylene glycol. With prolonged or high-dose intravenous administration, issues may arise related to the diluent used in the intravenous formulations, propylene glycol [84–86]. Signs and symptoms of propylene glycol toxicity include metabolic acidosis, renal failure/insufficiency, mental status changes, hemolysis, and an elevated osmolar gap. Propylene glycol is metabolized in the liver to lactic acid and pyruvic acid, which, in part, accounts for the lactic acidosis. Propylene glycol is also excreted unchanged in the urine making toxicity more likely in patients with renal insufficiency. Attention to the propylene glycol infusion rate and periodic calculation of the osmolar gap (measured minus calculated serum osmolarity) may be indicated during high dose or prolonged lorazepam infusions. An increasing osmolar gap has been shown to be predictive of increasing serum propylene glycol levels [86]. As neonates and preterm infants are unable to handle propylene glycol related to hepatic and renal immaturity, continuous infusions of lorazepam are not recommended in this population.

In a cohort of 11 PICU patients, who received lorazepam infusions ranging from 0.1 to 0.33 mg/kg/h for 3–14 days, the propylene glycol concentration increased from 86 ± 93 μg/mL at baseline to 763 ± 660 μg/mL at the completion of the infusion [87]. The plasma propylene glycol concentration correlated with the cumulative dose of lorazepam. No end-organ effects, related to the increased propylene glycol concentrations such as acidosis or hyperosmolarity, were noted in these patients. The authors recommended periodic monitoring for lactic acidosis and hyperosmolarity during prolonged lorazepam infusions

Etomidate

Etomidate (Amidate, Abbott Pharmaceuticals) is an intravenous anesthetic agent, introduced into clinical practice in 1972. Its primary effects of sedation and amnesia are mediated through the GABA inhibitory neurotransmitter system. Unlike other sedative and hypnotic agents, only the R(+) enantiomer has clinical effects. Following intravenous administration, loss of consciousness is rapid (15–20 s) and as with propofol and the barbiturates, its duration of action following a single bolus dose is related to redistribution rather than metabolism and clearance. Etomidate undergoes hepatic metabolism with an elimination half-life that varies from 2.9 to 5.3 h [88]. Beneficial CNS effects include a decrease of the cerebral metabolic rate for oxygen ($CMRO_2$), cerebral blood flow (CBF), and ICP. Cerebral perfusion pressure (CPP) is maintained because of minimal effects on myocardial function. In an animal model comparing the hemodynamic effects of an induction dose of etomidate (0.3 mg/kg) with propofol (2.5 mg/kg), no hemodynamic changes were noted with etomidate while propofol decreased systolic blood pressure by 19.9%, diastolic blood pressure by 25.3%, cardiac output by 17.3%, and systemic vascular resistance by 11.6% [89].

Contrary to a relatively large clinical experience in the adult population, there are limited data regarding the use of etomidate in pediatric-aged patients [90–93]. Despite the relatively limited clinical data regarding this agent, recent reviews continue to suggest its use as a single

bolus dose for critically ill pediatric patients requiring endotracheal intubation [94].

Like the barbiturates and propofol, etomidate results in a dose-dependent depressant effect on respiratory function and can result in apnea depending on the dose used, concomitant use of other medications, and the patient's underlying status. Lehman and Mainka evaluated the effects on CO_2 responsiveness of alfentanil (15 μg/kg) after premedication with etomidate (10 mg), diazepam (5 mg), or droperidol (5 mg) in adult volunteers [95]. All patients demonstrated a shift of the CO_2 response curve to the right without a change in the slope. These effects dissipated in 60 min. No difference was noted between etomidate and the other two premedications. Although both methohexital (1.5 mg/kg) and etomidate (0.3 mg/kg) decrease the slope of the CO_2 response curve, the effect has been shown to be more pronounced with methohexital [96]. Despite this relative sparing of respiratory function, an increased incidence of apnea has been reported following etomidate in patients pretreated with either opioids of benzodiazepines [97, 98].

Etomidate's place as an agent for procedural sedation results from its negligible effects on myocardial function, even in patients with significant alterations in myocardial function. It has beneficial effects on the CNS which include a reduction of the $CMRO_2$ leading to cerebral vasoconstriction, decreased CBF, and decreased ICP. Renou et al. noted a 34% decrease in CBF following the administration of etomidate in healthy adults [99]. As a result of the decreased $CMRO_2$ and CBF, etomidate decreases ICP while maintaining mean arterial pressure thereby increasing cerebral perfusion pressure [100]. Despite its ability to lower CBF and ICP, induction or sedative doses of etomidate can produce increased EEG activity and epileptic-like EEG potentials in patients with underlying seizure disorders [100–103].

Myoclonic movements are a frequently observed effect following the rapid intravenous administration of etomidate [104]. Although these movements may simulate tonic-clonic seizure activity, no epileptiform discharges are noted. It has been suggested that the myoclonic movements are of spinal origin resulting from disinhibition of inhibitory neuronal pathways. Pretreatment with fentanyl, benzodiazepines, or a small dose of etomidate has been shown to be effective in decreasing the incidence of myoclonus. A trial of etomidate for sedation during computerized tomography was discontinued due to an unacceptably high incidence of involuntary motor movements preventing completion of the scan [105]

The most significant concern with etomidate and the factor that limits its long-term administration in the ICU setting is its effects on the endogenous production of corticosteroids. This effect was identified when an increased risk of mortality was noted in adult ICU patients who were sedated with a continuous infusion of etomidate [106]. Etomidate inhibits the enzyme, 11-β hydroxylase, which is necessary for the production of cortisol, aldosterone, and corticosterone. To date, significant controversy surrounds the clinical significance of the adrenal suppression following a single induction dose of etomidate, with some authors calling for the abandonment or at least a reevaluation of the use of etomidate [107–109]. The duration of the adrenal suppression produced by a single induction dose of etomidate has varied from study to study.

Duthie et al. demonstrated a decrease in plasma cortisol levels 1 h following an induction dose of etomidate; however, at 24 h no difference was noted between those patients receiving etomidate and those receiving other induction agents [110]. Other authors have suggested a more prolonged suppression of adrenocortical function. Donmez et al. evaluated the effects of etomidate on plasma cortisol levels in children following cardiothoracic surgery [111]. The patients were randomized to anesthetic induction with either ketamine (1 mg/kg) or etomidate (0.3 mg/kg). Plasma cortisol levels were significantly lower during cardiopulmonary bypass, at the end of the operation, and at 24 h in the group that received etomidate vs. ketamine. Absalom et al. reported a similar effect with ongoing suppression of adrenal function at 24 h in a cohort of critically ill adult patients [112]. In a cohort of 40 critically ill adult patients, the incidence of adrenal insufficiency following a

single dose of etomidate was 80% at 12 h, 9% at 48 h, and 7% at 72 h [113]. Despite these findings, no difference in outcome was reported following etomidate administration in a cohort of 159 adult patients with septic shock [114].

Perhaps the most compelling data against the use of etomidate, at least in patients with possible sepsis, comes from the CORTICUS trial [115]. Post hoc analysis revealed that patients who had received etomidate had a significantly higher mortality rate. Additionally, this increased risk of mortality was not prevented by the administration of corticosteroids. These data suggest that etomidate should be avoided in patients with sepsis or septic shock.

In addition to its effects on adrenal function, reports regarding continuous etomidate infusions with increased mortality suggested an association with infectious complications. Neutrophils incubated in vitro with etomidate demonstrate depressed chemiluminescence, an index of oxygen-free radical generation, suggesting that etomidate may interfere with white blood cell bactericidal activity [116].

Additional reported adverse effects with etomidate, related to the drug itself or the diluent, include anaphylactoid reactions, pain on injection, and an increased incidence of nausea and vomiting [117]. Issues related to the carrier vehicle (propylene glycol) include pain on injection, thrombophlebitis, and propylene glycol toxicity [118]. The incidence of pain on injection has been reported to be as high as 50%.

A newer formulation, which contains etomidate dissolved in a fat emulsion of medium and long-chair triglycerides, may limit the occurrence of injection pain and thrombophlebitis [119]. As with lorazepam, issues may arise with repeated dosing or continuous infusions of etomidate because of the diluent, propylene glycol (please note that given concerns regarding adrenal suppression, long-term etomidate infusions are no longer used in the ICU setting) [120–122].

Despite these issues, given its beneficial effects on CNS dynamics and myocardial function, etomidate has yet to be abandoned in critically ill patients and may still play a role as an effective agent to provide sedation and amnesia during endotracheal intubation [123]. Its lack of cardiovascular effects makes it particularly valuable in patients who may not tolerate a decrease in systemic vascular resistance or myocardial contractility. Given its effects on cerebral dynamics, it also should be considered for patients with increased ICP with or without associated myocardial dysfunction. Although of limited utility for the provision of procedural-sedation outside of endotracheal intubation, as with several other sedative/analgesic agents, nonintravenous routes of delivery including oral, buccal and rectal administration have been investigated [124–126].

Ketamine

Ketamine was introduced into clinical practice during the 1960s [127]. Ketamine's sedative, analgesic, and amnestic properties are mediated through agonism of opioid receptors and antagonism of NMDA receptors. A unique attribute of ketamine, which separates it from the majority of other agents discussed in this chapter, is the provision of both amnesia and analgesia. Ketamine contains a chiral carbon in its structure and the preparation currently used most commonly in clinical practice is a racemic mixture of the two optical isomers [S(+) and R(−)].

In the United Kingdom and Europe, the enantiomer, S(+) ketamine, is available with the suggestion from preliminary clinic trails that it may provide effective analgesia and sedation while limiting adverse effects including emergence phenomena (see below). Metabolism of ketamine occurs primarily by hepatic *N*-methylation to norketamine, which retains approximately one third of the analgesic and sedative properties of the parent compound. Given its dependence on hepatic metabolism, doses should be adjusted in patients with hepatic dysfunction. Dose adjustments may also be required in patients with renal dysfunction since norketamine is dependent on renal elimination.

Beneficial properties of ketamine include preservation of cardiovascular function, limited effects on respiratory mechanics, and maintenance of central control of respiration. These properties make it an effective and popular agent in the arena of procedural sedation during painful, invasive procedures in the spontaneously

breathing patient [10]. Incremental doses (0.5–1 mg/kg) can be administered every 1–2 min and titrated to achieve the desired level of sedation and analgesia while generally maintaining spontaneous ventilation.

Given its effects at the opioid and NMDA receptors, there is growing interest in the use of ketamine for the management of acute pain. When coadministered in low doses during morphine analgesia, ketamine has been shown to reduce postoperative opioid consumption and lower opioid-related adverse effects following major surgical procedures in the adult population [128–131]. As NMDA receptor stimulation may be one factor resulting in the development of tolerance to opioid-induced sedation and analgesia, there is interest in the potential benefits of using a low-dose ketamine infusion to delay tolerance during prolonged ICU infusions of morphine and other opioids.

Ketamine's popularity in the arena of procedural-sedation, especially painful invasive procedures, relates to its beneficial effects on cardiac and respiratory function. Ketamine generally increases heart rate and blood pressure as well as provides bronchodilatation due to the release of endogenous catecholamines [132]. Although the indirect sympathomimetic effects from endogenous catecholamine release generally overshadow ketamine's direct negative inotropic properties, cardiovascular collapse may occur in patients with diminished myocardial contractility [133, 134].

An issue of potential concern and ongoing controversy regarding ketamine is its effects on pulmonary vascular resistance (PVR) [135–138]. Williams et al. evaluated the effects of ketamine on PVR during sevoflurane anesthesia (0.5 MAC) and spontaneous ventilation in 15 infants and children with pulmonary hypertension (mean PA pressure ≥25 mmHg, baseline PVR index of 11.3 Woods units) [139]. There were no significant changes in mean systemic arterial pressure, systemic vascular resistance index, mean pulmonary artery pressure, PVR index, cardiac index, and $PaCO_2$. The safety of ketamine in patients with congenital heart disease is further evidenced by experience with its use during spontaneous ventilation for sedation during cardiac catheterization [140, 141].

Ketamine has also been shown to have limited effects on several respiratory parameters including functional residual capacity, minute ventilation, and tidal volume [142, 143]. The release of endogenous catecholamines generally results in improved pulmonary compliance, decreased resistance, and prevention of bronchospasm [144, 145]. Although generally effective in allowing maintenance of protective airway reflexes and spontaneous ventilation, like any sedative/analgesic/general anesthetic agent, ketamine can result in loss of protective airway reflexes, gastric aspiration, and apnea [146–148].

An additional area of controversy surrounding ketamine is its effect on ICP. These effects may be indirect, secondary to changes in $PaCO_2$, or the result of a direct effect on the cerebral vasculature [149–152]. More recent data from both animal and human studies have shown no change or even a decrease in ICP following ketamine [153, 154].

Ketamine in doses of 1.5, 3, or 5 mg/kg decreased ICP when administered to adult head trauma patients who were sedated with propofol and mechanically ventilated to maintain a $PaCO_2$ of 35–38 mmHg [155]. The ICP decreased by 2 ± 0.5, 4 ± 1, and 5 ± 2 mmHg with doses of 1.5, 3, and 5 mg/kg respectively. There was no change in CPP. Similar results were reported by others [156, 157].

An additional potentially beneficial effect of ketamine in patients with CNS trauma is an alteration of transmembrane calcium and magnesium currents through its effects on the NMDA receptor [158].

Another somewhat controversial issue related to the CNS effects of ketamine is its use in patients with an underlying seizure disorder. EEG recordings in children and laboratory animals during ketamine administration demonstrate increased frequency and amplitude with occasional paroxysmal seizure activity [159, 160]. However, no clinical evidence of seizure activity has been reported with ketamine administration. Studies in laboratory animals have demonstrated the anticonvulsant effects of ketamine and there is at least one clinical report as well as animal data describing its use for the treatment of refractory status epilepticus [161–163].

With everyday clinical use, the adverse effect of ketamine that tends to attract the most attention is its potential to cause emergence phenomena or hallucinations. The ketamine solution that is in common clinical use is a racemic mixture of the two optically active enantiomers. The single enantiomer form, S(+) ketamine, has been released outside of the United States for clinical use [164–167]. The initial clinical trials have demonstrated that S(+) ketamine is twice as potent as the racemic formulation and offers the clinical advantages of fewer psychomimetic effects, less salivation, and a shorter recovery time [167].

To date, there are only anecdotal reports involving small case series regarding the use of a ketamine infusion for sedation of the PICU patient during mechanical ventilation [168–170]. The largest series included ten patients, ranging in age from 1 week to 30 months. A ketamine infusion, 1 mg/kg/h in five patients and 2 mg/kg/h in the other five patients, was used to provide sedation and analgesia following cardiac surgery in ten pediatric patients [169]. Supplemental doses of midazolam were administered as needed. The two groups had similar and acceptable levels of sedation. No adverse effects were noted.

Although it may never become a first-line agent for sedation in the PICU patient during mechanical ventilation, ketamine may be useful in patients who develop adverse cardiovascular effects with opioids or benzodiazepines, for the provision of sedation with the preservation of spontaneous ventilation when using noninvasive ventilation techniques, in patients with status asthmaticus in whom the release of endogenous catecholamines following ketamine administration may provide some therapeutic impact, in low doses by continuous infusion to delay or prevent the development of tolerance to opioids related to its effects at the NMDA receptor, and during the performance of brief, painful invasive procedures in the spontaneously breathing patient [166, 171, 172].

Propofol

Propofol is an alkyl phenol compound (2,6-diisopropylphenol) with general anesthetic properties. Although its chemical structure is distinct from that of other intravenous anesthetic, its mechanism of action is similar as it acts through the GABA system [173]. Propofol facilitates the binding of GABA to membrane-bound receptors thereby increasing chloride conductance. Although propofol was initially introduced into anesthesia practice for the induction and maintenance of anesthesia, its rapid onset and recovery times led to its eventual use for sedation in the ICU setting [174, 175]. When compared with midazolam for sedation in adult patients, propofol has been shown to provide shorter recovery times, improved titration efficiency, reduced posthypnotic obtundation, and faster weaning from mechanical ventilation [176].

Like the barbiturates and etomidate, propofol decreases $CMRO_2$ leading to reflex cerebral vasoconstriction and lowering of ICP [177].

Several animal studies have confirmed the potential beneficial effects of propofol on cerebral dynamics. In an animal model of cytotoxic and vasogenic cerebral edema, propofol lowered ICP and maintained CPP in vasogenic cerebral edema, but had no effect in cytotoxic cerebral edema [178]. Watts et al. compared the effects of propofol and hyperventilation on ICP and somatosensory evoked potentials (SEPs) in an animal model of intracranial hypertension [179]. The ICP decrease and the SEP increase were greater with propofol than with hyperventilation.

Despite these animal data, there are conflicting results in regard to the effects of propofol on ICP from studies in humans. Although ICP is decreased in the majority of the studies, propofol's lowering of MAP may result in a decrease of the CPP [180]. Similar results have been reported in adults with traumatic brain injury or during cerebral aneurysm surgery [181–183].

If MAP is maintained at baseline with vasoactive agents, propofol may lower ICP and increase CPP. When propofol (2–4 mg/kg/h) was used for sedation during mechanical ventilation in ten adult patients with traumatic brain injury, ICP decreased by a mean of 2.1 mmHg at 2 h and the CPP increased by 9.8 mmHg at 24 h [184]. Additional beneficial effects of propofol in brain injury include animal data suggesting a protective effect of propofol in various types of

hypoxic-ischemic injury models as well as the preservation of the CBF reactivity to carbon dioxide [185–187].

When comparing the effects of propofol (2.5 mg/kg), etomidate (0.4 mg/kg), or thiopental (5 mg/kg) in 77 adults, respiratory resistance was lower after propofol [188]. Pizov et al. randomized a cohort of asthmatic and nonasthmatic patients to receive thiopental/thiamylal (5 mg/kg), methohexital (1.5 mg/kg), or propofol (2.5 mg) [189]. Following endotracheal intubation, auscultation was performed. In asthmatic patients, the incidence of wheezing was 45% with thiopental/thiamylal, 26% with methohexital, and 0% with propofol. In nonasthmatic patients, the incidence of wheezing was 16% with thiopental/thiamylal and 3% with propofol. Propofol's beneficial effects on airway reactivity are further supported by animal studies [190, 191]. In both an animal model and a human study, these beneficial effects were present only with the propofol solution that has ethylenediaminetetraacetic acid (EDTA) as the preservative and not the newer formulation containing sodium metabisulfite [192, 193].

Propofol's cardiovascular effects resemble those of the barbiturates with the potential for hypotension from peripheral vasodilation and negative inotropic properties. These effects are dose-dependent and can be accentuated following rapid bolus administration and in patients with compromised cardiovascular function. The adverse hemodynamic profile of propofol administration can be prevented by the administration of calcium chloride [194]. Additional cardiovascular effects may be caused by augmentation of central vagal tone leading to bradycardia, conduction disturbances, and asystole [195–197]. These effects are more likely with the concomitant administration of other medications known to alter cardiac chronotropic function including fentanyl or succinylcholine.

Various neurological manifestations have been reported with the administration of propofol including opisthotonic posturing, myoclonic movements (especially in children), and movements that may resemble seizure-like activity [198–200]. Myoclonus, opisthotonic posturing, and other movements with propofol have been attributed to propofol's antagonism at glycine receptors in subcortical structures. To date, there is no formal evidence linking propofol with seizures [201]. Propofol remains an effective agent for the termination of refractory status epilepticus and remains in various published algorithms regarding recommendations for its treatment [202, 203].

Despite its potential benefits in the ICU setting and its efficacy for providing sedation during mechanical ventilation, the routine use of propofol is not recommended and, in fact, is considered contraindicated by many authorities because of the potential for the development of what has been termed the "Propofol Infusion Syndrome." First described in 1992 by Parke et al., the disorder includes metabolic acidosis, bradycardia, dysrhythmias, rhabdomyolysis, and fatal cardiac failure [204–206]. Eighteen children in the ICU setting with suspected propofol infusion syndrome were reviewed in a report by Bray [207]. The risk factors in the cohort for the development of the syndrome included propofol administration for ≥48 h or an infusion rate ≥4 mg/kg/h. However, not all patients meeting these risk factor criteria developed problems, suggesting that comorbid diseases or a genetic predisposition may be responsible for the development of the Propofol Infusion Syndrome. Additionally, 13 of the 18 patients were ≤4 years of age while only one was ≥10 years of age. Subsequent to the initial reports and the review of Bray et al., the syndrome has been reported in older patients including a 17-year-old adolescent and adults [208–210]. In addition to the metabolic acidosis and cardiovascular manifestations, additional clinical findings have included lipemic serum, hepatomegaly, rhabdomyolysis, and hyperkalemia.

The suggested treatment for Propofol Infusion Syndrome includes the immediate discontinuation of the propofol combined with symptomatic treatment of cardiovascular dysfunction and acidosis. Reports in animals and humans suggest that this syndrome is related to a disruption in mitochondrial function [211–213]. Anecdotal evidence suggests that hemodialysis may be helpful as a therapeutic tool by removing a yet undiagnosed metabolite or toxin [212, 213].

Despite these concerns, it appears that the contention that we should abandon the use of propofol for sedation during mechanical ventilation in the PICU setting has not been universally embraced. Although propofol has been used safely and effectively for sedation in small cohorts of PICU patients [214–218], the decision to use propofol should be considered in context of the "Dear Healthcare Provider" letter issued in March 2001 by AstraZeneca (Wilmington, DE), the manufacturers of Diprivan®, one of the commercially available propofol preparations [219]. The letter summarizes the results of a prospective clinical trial which compared propofol (a 1 or 2% solution) to other agents used for PICU sedation. There were 12 (11%) deaths in the 2% propofol group, 9 deaths (8%) in the 1% propofol group, and 4 deaths (4%) in the standard sedation group. Although subsequent review did not show a specific pattern to the deaths, there was enough concern that the company issued a letter stating: "propofol is currently not approved for sedation in PICU patients in the United States and should not be used for this purpose." In many centers, these concerns have eliminated the prolonged use of propofol for sedation in the PICU.

In specific clinical scenarios, propofol is still used as a therapeutic tool in the treatment of refractory status epilepticus or increased ICP. In such cases, intermittent analysis of acid–base status and creatinine phosphokinase is suggested. If a base deficit is noted with an increasing serum lactate, immediate discontinuation of the propofol is recommended. Additionally, the short-term administration of propofol (6–12 h) is still used in many centers to transition from other agents such as fentanyl and midazolam to allow for more rapid awakening for tracheal extubation. Short-term propofol infusions may also have a role in the arena of procedural sedation as a means of providing sedation during nonpainful invasive procedures such as radiologic imaging. Although rare, when such procedures are long, concern has also been expressed regarding the potential development of the Propofol Infusion Syndrome [220].

Additional concerns with propofol regarding its use for procedural sedation in spontaneously ventilating patients include a relatively high incidence of respiratory effects including hypoventilation, upper airway obstruction and progression to general anesthesia and apnea, many of which required bag-mask ventilation or repositioning of the airway [221, 222].

As propofol is delivered in a lipid emulsion, there may be allergic reactions, pain on injection, and elevated triglyceride levels or hypercapnia with prolonged infusions [223–225]. Cross-reactivity may occur in patients with allergies to egg, egg products, soy beans, or soy products. A propofol infusion of 2 mg/kg/h provides approximately 0.5 g/kg/day of fat. To limit the impact of the lipid component, a 2% solution of propofol (twice the amount of propofol with the same amount of lipid per mL as the 1% solution) has undergone clinical evaluations [226–229]. Given the concerns regarding the lipid component, its fat content should be considered into daily caloric requirements if prolonged infusions are used.

Pain with the injection of propofol remains a significant complaint especially when small veins on the dorsum of the hands or feet are used. Variable success in decreasing the incidence of pain has been reported with various maneuvers including the preadministration of lidocaine, mixing the lidocaine and propofol in a single solution, mixing the propofol with thiopental, diluting the concentration of the propofol, cooling it prior to bolus administration, or the administration of a small dose of ketamine (0.5 mg/kg) prior to the administration of propofol [230–234].

One final issue with the lipid component of propofol is its potential to serve as a viable growth media for bacteria with reports of bacteremia and postoperative wound infections linked to extrinsically contaminated propofol [235, 236]. Various preservatives are used in the currently available propofol solutions including disodium EDTA or sodium metabisulfite. In clinical practice, there may be subtle yet clinically significant differences in these preparations, including differential effects on airway reactivity which have already been discussed in this chapter [192, 193]. Trissel et al. have provided preliminary information that the compatibility of various medications is different with the two propofol preparations [237]. This is an important issue for pediatric

patients in whom intravenous access may be limited. The literature contains contrasting information regarding the anesthetic potency of the two preparations [238–239]. A theoretical disadvantage of disodium EDTA is the chelation and depletion from the body of essential trace minerals such as zinc. Although there are no formal studies to demonstrate that this is a problem, concerns related to this issue are outlined in the manufacturer's package insert.

Barbiturates

The barbiturates were first synthesized in 1864 by von Baeyer. Thiopental, a short-acting barbiturate was first administered for clinical use in 1934. This class of anesthetic agent can be classified according to their chemical structure or their duration of activity. Short-acting agents such as methohexital, thiopental, and thiamylal have a clinical duration of action of 5–10 min and are used most commonly as a single bolus dose for the induction of anesthesia. When a more prolonged effect is needed, a continuous infusion may be used to maintain constant plasma levels. Long-acting agents with half-lives of 6–12 h include pentobarbital and phenobarbital. The clinical effects of the short-acting agents dissipate rapidly related to their redistribution, although their hepatic metabolism may take hours. However, when this is done, the offset time will also be markedly prolonged and dependent on the duration of the infusion.

In the PICU setting, the barbiturates are occasionally used by continuous infusion for sedation during mechanical ventilation (see below) although their more common use is based on their beneficial physiologic and therapeutic effects as anticonvulsants or to decrease ICP in patients with traumatic brain injury [240–245].

The ultra-short-acting barbiturates (thiopental and thiamylal) are used clinically in a 2.5% solution with a pH 10.5. The high pH results in a bacteriostatic solution limiting concerns of bacterial contamination as well as limiting the pain that may occur with intravenous injection. However, the pH of 10.5 leads to incompatibilities with other medications and parenteral alimentation solutions, thereby necessitating a separate infusion site if a continuous infusion is used. Of particular note is the potential for the barbiturates to form precipitates when administered with drugs such as rocuronium, mandating flushing the line during the rapid administration of medications during maneuvers such as rapid sequence intubation (to avoid loss of intravenous access during critical moments). Local erythema, thrombophlebitis, or skin sloughing may occur with subcutaneous infiltration. The barbiturates possess no analgesic properties and therefore should be used with an opioid in situations requiring analgesia.

The barbiturates' place in ICU sedation appears to be an alternative or second-line agent when primary agents, either alone or in combination, fail to provide adequate sedation or result in untoward side effects [246]. There are a limited number of reports regarding the use of pentobarbital infusions for sedation in the PICU setting. A retrospective report described the use of pentobarbital for sedation during mechanical ventilation of 50 infants and children, ranging in age from 1 month to 14 years [247]. Pentobarbital was administered for a median duration of 4 days (range 2–37 days) at a median dose of 2 mg/kg/h (range 1–6 mg/kg/h). The cohort included seven non-neonatal ECMO patients in whom pentobarbital provided effective sedation. Tolerance was noted with the administration of pentobarbital. In the 14 patients who received pentobarbital for ≥5 days, the dose requirements increased from 1.2 mg/kg/h on day #1 to 3.4 mg/kg/h on day #5. No significant adverse effects related to pentobarbital were noted. Six of the 36 patients who had received pentobarbital for more than 4 days manifested signs and symptoms of withdrawal.

Yanay et al. reported their retrospective experience with pentobarbital sedation for eight PICU patients [248]. Although pentobarbital provided effective sedation and allowed the discontinuation of neuromuscular blocking agents, they noted a relatively high incidence of adverse effects including blood pressure instability (25%), oversedation (12.5%), and neurologic sequelae (12.5%) including withdrawal phenomena. These adverse effects led to discontinuation of the drug in 25% of their patients.

In addition to their role for therapeutic agents or perhaps for the provision of sedation during mechanical ventilation, there are several reports outlining the use of various barbiturates for procedural sedation. As they have no intrinsic analgesic properties, the barbiturates are used most commonly for sedation during nonpainful procedures.

The short-acting oxybarbiturate, methohexital, has been used extensively via both oral and PR route as a sedative for CT or MR imaging with success rates of up to 80–85% [249]. The standard dose per rectum is 20–30 mg/kg, which produces a rapid onset of sleep (6–10 min) with recovery to baseline status within 1.5–2 h. Adverse effects are uncommon with mild respiratory depression responsive to repositioning or the administration of supplemental oxygen occurring in up to 4% of patients. The duration of action with intravenous use (0.75–1.0 mg/kg) is approximately 10 min, making the drug attractive for short procedures such as CT imaging. However, the incidence of respiratory depression is greater with the intravenous route of administration, which may limit its usefulness. Unlike the other barbiturates, methohexital may activate the EEG and has been reported to precipitate seizures in patients with underlying seizure disorders.

Although used most commonly by the intravenous route for the induction of anesthesia, thiopental has also been used as a rectal agent for sedation for radiologic procedures in doses of 25–50 mg/kg [250, 251]. When compared with methohexital, the depth of sedation achieved and reported success rates were somewhat higher (>90%). The onset of action is slightly longer (15–30 min) with a similar duration of action (60–90 min) compared to methohexital.

Pentobarbital has an intermediate duration of action and remains a popular choice for intravenous sedation during radiologic procedures such as MR imaging where sedation times may approach 60–90 min. Multiple delivery options are available including the IV, IM, and enteral routes, although IV administration remains the most commonly used route. Pentobarbital is administered in increments of 1–2 mg/kg every 3–5 min until sleep is induced (average total dose 4–5 mg/kg) [252, 253]. The average duration of sleep after a single intravenous dose is 60–90 min, which is adequate to perform most routine MRI evaluations. Respiratory depression and hypotension may occur, especially with rapid intravenous administration. Disadvantages with pentobarbital include prolonged recovery times (2–4 h) and emergence issues including agitation.

Opioids

Although generally used for analgesia, opioids also possess sedative properties; especially those with agonistic effects at the κ opioid receptor [254]. Therefore, these agents may be effective for providing sedation during mechanical ventilation and remain second to the benzodiazepines as the most commonly used agents in the PICU setting. Although the opioids provide analgesia, amnesia is not ensured. Therefore, additional agents are required in situations which demand amnesia such as the patient who is receiving a neuromuscular blocking agent. In patients with altered myocardial function or at risk for pulmonary hypertension (such as an infant with a large preoperative left-to-right shunt), the synthetic opioids have been shown to provide cardiovascular stability, beneficial effects on pulmonary vascular resistance, and blunting of sympathetic stress response. Due to their prompt redistribution and resultant short plasma half-lives following bolus administration, the synthetic opioids are generally administered by a continuous infusion to maintain plasma concentrations adequate to provide sedation and analgesia.

The synthetic opioids that are currently in common clinical use include fentanyl, sufentanil, alfentanil, and remifentanil. Fentanyl is the least expensive of the synthetic opioids and the one with which there is the most clinical experience in the PICU setting. Fentanyl, sufentanil, and alfentanil are dependent on hepatic metabolism. Although these agents are short acting when administered as a single bolus dose, they also have a context-sensitive half-life, so that the duration of their effect is prolonged when they are administered over an extended period of time.

Unlike the other opioids which undergo hepatic metabolism, remifentanil is metabolized by nonspecific esterases in the plasma. It has a clinical half-life of 5–10 min and a brief duration of effect even following 12–24 h of continuous infusion [255]. These pharmacokinetic parameters hold true even in the neonatal population, making remifentanil the only opioid whose pharmacokinetics is not altered by gestational or chronologic age [256]. Given these properties, it is a potentially useful agent for providing a deep level of sedation and yet allowing for rapid awakening with discontinuation of the infusion even in the neonatal population. To date, there remains limited experience with its use in the ICU population.

Cavaliere et al. evaluated the efficacy of a remifentanil infusion in doses starting at 0.02 μg/kg/min and increasing up to 0.25 μg/kg/min, in providing sedation during mechanical ventilation in a cohort of ten adult ICU patients [257]. Although sedation, assessed by clinical sedation scales, was adequate in the ten patients, the maximum infusion rate was achieved in only 4 of the 10 patients due to the occurrence of adverse effects including hypotension and bradycardia at infusion rates ≥0.15 μg/kg/min. Hypoventilation was noted at infusion rates as low as 0.1 μg/kg/min.

In a prospective, randomized trial, adults requiring mechanical ventilation received either a morphine infusion at 0.75 μg/kg/min or a remifentanil infusion at 0.15 μg/kg/min [258]. The percentage of optimal sedation hours was significantly greater with remifentanil. There was no difference in the incidence of adverse effects.

To date, there are only anecdotal reports regarding the use of remifentanil for sedation during mechanical ventilation in the PICU population [259].

An issue that needs further investigation prior to its widespread application in the ICU setting is the rapid development of tolerance. In adult volunteers, tolerance to remifentanil may develop after only 60–90 min [260]. This has translated into the need to escalate doses rapidly when remifentanil is used for ICU sedation [259–261]. Although tolerance may limit prolonged remifentanil infusions, there remains interest in the use of remifentanil in the arena of procedural sedation given that its effects dissipate rapidly when the infusion is discontinued [262–264]. Remifentanil has been combined with midazolam or propofol for painful, invasive procedures such as bronchoscopy or for fiberoptic intubation of the trachea [263].

Two additional issues relevant to the synthetic opioids are potential effects on ICP and the risks of chest wall rigidity. Anecdotal reports suggested the potential for the synthetic opioids to increase ICP and decrease CPP in adults with altered intracranial compliance [265]. Rather than a direct effect, the mechanism responsible for the ICP increase has been shown to be a reflex cerebral vasodilation in response to the decrease in mean arterial pressure or CPP [266].

A second adverse effect specific to the synthetic opioids is chest wall and laryngeal rigidity [267, 268]. These effects are related to the dose and the rate of administration. They are centrally mediated responses which can interfere with respiratory function. The incidence can be decreased by premedication with the α_2-adrenergic agonists, reversed with naloxone, and interrupted with neuromuscular blocking agents. Although rare, its occurrence should be considered if respiratory dysfunction is noted following the use of synthetic opioids.

Given issues with the rapid development of tolerance following the use of the synthetic opioids, morphine has regained popularity for sedation and analgesia during mechanical ventilation in the PICU setting. Given that morphine has agonistic effects at both the mu and the kappa opioid receptor, it provides not only analgesia via the mu receptor but also sedation via the kappa receptor. Cardiovascular effects include dilation of the venous capacitance system with a decrease in preload which may result in a modest decrease in blood pressure, especially in patients with decreased intravascular volume or comorbid cardiac diseases.

When used by continuous infusion for sedation during mechanical ventilation in neonates, morphine has been shown to have no effect on intelligence, motor function, or behavior [269]. In infants, morphine infusions of 10–30 μg/kg/h provided effective analgesia and sedation during

mechanical ventilation after surgery for congenital heart disease without impairing the ability to wean mechanical ventilatory support [270]. Morphine infusions blunt the sympathetic response and reduce epinephrine levels in neonates requiring endotracheal intubation and mechanical ventilation for hyaline membrane disease [271].

In a cohort of infants requiring sedation and analgesia during ECMO (mean duration of ECMO 4–5 days), morphine and fentanyl provided equivalent levels of sedation while decreasing the need for supplemental bolus doses of opioid [272]. Infants receiving morphine had a lower incidence of withdrawal (13 of 27 with fentanyl vs. 1 of 11 with morphine, $p<0.01$) and were hospitalized for fewer days after ECMO (31.1 ± 14 vs. 21.5 ± 7.0 days, $p=0.01$).

Although administered most commonly via the intravenous route, rare circumstances such as limited intravenous access or drug incompatibilities may occur which preclude intravenous administration in the PICU setting. In such situations, the subcutaneous administration of opioids is feasible [72, 273–276].

As with all of the previously described agents, opioids may have adverse effects on respiratory function with the potential for hypoventilation or apnea. However, an effect which appears to be relatively specific to the opioids is their potential impact on immune function [277–279]. Opioid receptors have been found on immune cells which participate in the inflammatory response and various host defenses [278, 279]. Although there are no studies directly linking these effects to adverse clinical outcomes, additional studies are needed to define these effects, their mechanisms, and most importantly their impact on the PICU patient.

Phenothiazines and butyrophenones

The phenothiazines and butyrophenones are classified as the "major tranquilizers." The majority of their clinical use is in the treatment of psychiatric disturbances or as antiemetics in various clinical scenarios. Of the several agents available, haloperidol is the agent that has been used most frequently for the sedation of adults in the ICU setting. Haloperidol acts through central dopamine receptors. With intravenous administration, its onset of action is within 10–20 min with a duration of action of 12–24 h given its long elimination half-life of 18–26 h [280]. Although not formally approved by the FDA for intravenous administration, there is an abundance of clinical experience with its use by this route [281].

Riker et al. reported their experience with the continuous infusion of haloperidol in doses ranging from 3 to 25 mg/h for sedation in eight adult ICU patients [282]. They proposed various benefits of haloperidol including a rapid onset, minimal respiratory depression, and lack of active metabolites.

A retrospective report regarding haloperidol use in a cohort of 989 adult patients, who required mechanical ventilation for more than 48 h, reported not only efficacy in controlling agitation and delirium but also a lower overall in-hospital mortality in patients who received haloperidol [283].

Experience with haloperidol in the PICU population remains anecdotal. Harrison et al. reported their experience with haloperidol, administered by intermittent bolus dosing to five critically ill children (9 months to 16 years) who had become difficult to sedate despite escalating doses of benzodiazepines and opioids [284]. Haloperidol's efficacy was demonstrated by a reduction of opioid and benzodiazepine requirements, decreased need for supplemental doses of sedative agents, decreased use of neuromuscular blocking agents, and improved clinical sedation. One patient developed a dystonic reaction which resolved in 36 h without therapy as the haloperidol had already been discontinued.

Potential adverse effects associated with the butyrophenones and phenothiazines include hypotension related to peripheral α-adrenergic blockade, dystonic and extrapyramidal effects, lowering of the seizure threshold, the neuroleptic malignant syndrome, and cardiac arrhythmias including *torsades de pointes* due to effects on cardiac repolarization [282]. The potential for cardiac dysrhythmias due to alterations in repolarization may be exacerbated in critically ill patients with altered sympathetic function related to fever, pain, or the stresses of an acute illness.

Similar issues may occur with other drugs of this class including droperidol [285].

Through a black box warning issued by the United States Food and Drug Administration, concern has been expressed regarding the potential association of droperidol and postoperative cardiac events including *torsades de pointes* in adult patients [286]. Prolonged postoperative ECG monitoring is suggested in patients treated with droperidol during the perioperative period.

Alpha$_2$-adrenergic agonists

Although used initially for clinical effects such as the control of blood pressure, the α_2-adrenergic agonists including clonidine and dexmedetomidine may also have a role in the PICU patient for the provision of sedation during mechanical ventilation, reduction of opioid requirements, the control of pain of various etiologies, and provision of sedation during noninvasive procedures. The physiologic effects of these agents are mediated via stimulation of postsynaptic α_2-adrenergic receptors [287–290]. Activation of receptors in the medullary vasomotor center reduces norepinephrine turnover and decreases central sympathetic outflow resulting in alterations in sympathetic function with decreased heart rate and blood pressure.

Additional effects result from the central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus cereleus in the brainstem. The latter effect plays a prominent role in the sedation and anxiolysis produced by these agents as decreased noradrenergic output from the locus cereleus allows for increased firing of inhibitory neurons including the GABA system, resulting in sedation and anxiolysis [291]. This effect has been shown to be similar to that which occurs during non-REM sleep [292, 293]. The lack of non-REM sleep with the use of other sedative agents including propofol, benzodiazepines, and barbiturates is one of the factors that may result in delirium in adult ICU patients. The α_2-adrenergic agonists also potentiate the analgesic effects of opioids by regulating substance P release within the central nervous system.

Clonidine has been used as a premedicant in the operating room, for caudal and epidural analgesia, as an adjunct to opioid-induced analgesia during the postoperative period, and even for ICU sedation [294–298]. Although initially available only as a tablet, clonidine is now available as a transdermal patch and as a preparation for neuraxial administration. The latter has been administered intravenously in various clinical scenarios.

In an open label evaluation in children in the PICU setting, a continuous clonidine infusion starting at 1 μg/kg/min was added to a continuous midazolam infusion of 1 μg/kg/min [298]. No significant changes in heart rate, blood pressure, or cardiac index were noted. In 2 of the 20 patients, the clonidine infusion was increased to 2 μg/kg/h. The clonidine infusion provided adequate sedation for 602 of the 672 study hours with no sedation failures.

Arenas-Lopez et al. reported their experience with the addition of enteral clonidine (3–5 μg/kg every 8 h) as an adjunct to intermittent doses of morphine and lorazepam for sedation during mechanical ventilation in 14 children [299]. Adequate sedation was achieved during 82% of the study period with an overall decrease in the requirements for both lorazepam and morphine. No adverse effects were noted.

More recently, dexmedetomidine has been released for clinical use and sedation [300–302]. Like clonidine, it is a centrally acting, α_2-adrenergic agonist and exhibits the same physiologic effects. However, it possesses an affinity 8 times that of clonidine for the α_2-adrenergic receptor, a differential α_1 to α_2 agonism of 1:1,600, and a half-life of 2–3 h thereby allowing its titration by intravenous administration.

In healthy adult volunteers, the pharmacokinetic profile of dexmedetomidine includes a rapid distribution phase with a distribution half-life of approximately 6 min, an elimination half-life of 2 h. Dexmedetomidine exhibits linear kinetics, is 94% protein bound, and undergoes hepatic metabolism with minimal unchanged drug excreted in the urine and feces. Given its dependence on hepatic metabolism, dose adjustments are necessary in patients with altered hepatic function.

To date, there is only one prospective trial evaluating dexmedetomidine for sedation during mechanical ventilation in pediatric-aged patients

[303]. Efficacy was evaluated using the Ramsay Scale and by comparing the requirements for supplemental morphine. Dexmedetomidine at 0.25 μg/kg/h provided sedation that was equivalent to midazolam at 0.22 mg/kg/h. Dexmedetomidine at 0.5 μg/kg/h was more effective than midazolam as demonstrated by a decreased need for supplemental morphine and a decrease in the number of Ramsay scores of 1 exhibited by the patients. Dexmedetomidine was somewhat less effective in patients ≤12 months of age as 5 of the 6 patients who exhibited a Ramsay score of 1 during dexmedetomidine were less than 12 months of age. The only adverse effect was bradycardia in one patient receiving dexmedetomidine who was also receiving digoxin [304].

In addition to its use for sedation during mechanical ventilation, other applications of dexmedetomidine have included procedural sedation, prevention of shivering, and treatment of iatrogenic opioid and benzodiazepine withdrawal following prolonged use in the ICU setting [300].

Koroglu et al. randomized 80 children (1–7 years of age) to dexmedetomidine or midazolam during MR imaging [305]. Dexmedetomidine was administered as a loading dose of 1 μg/kg over 10 min followed by an infusion of 0.5 μg/kg/h while midazolam was administered as a loading dose of 0.2 mg/kg followed by an infusion of 6 μg/kg/h. The quality of sedation was better and the need for rescue sedation was less (8 of 40 vs. 32 of 40) with dexmedetomidine compared to midazolam. Similar efficacy was reported in an open label trial of dexmedetomidine for sedation during MR imaging in 48 pediatric patients ranging in age from 5 months to 16 years [306]. Fifteen patients had failed chloral hydrate and/or midazolam and 33 patients received dexmedetomidine as the primary agent. The mean loading dose of dexmedetomidine to initiate sedation was 0.92 ± 0.36 μg/kg. This was followed by an infusion of 0.69 ± 0.32 μg/kg/h. Effective sedation was achieved in all patients and the scan was completed without other agents. Recovery time was longer in patients who had received other agents prior to dexmedetomidine than in those who received dexmedetomidine as a primary agent (117 ± 41 vs. 69 ± 34 min).

A second study by Koroglu et al. randomized 60 children to dexmedetomidine or propofol during MR imaging [307]. Although both of the agents were equally effective in providing sedation, propofol provided shorter induction times, recovery times, and discharge times. However, adverse effects including hypotension and oxygen desaturation were more common with propofol. Oxygen desaturation requiring intervention including a chin lift, discontinuation of the infusion, or supplemental oxygen occurred in 4 of 30 children receiving propofol vs. 0 of 30 receiving dexmedetomidine.

In a retrospective review of their Quality Assurance database, Mason et al. used escalating doses of dexmedetomidine for sedation in 62 children during radiological imaging [308]. Dexmedetomidine was administered as a loading dose of 2 μg/kg over 10 min and repeated to achieve effective sedation after which an infusion was started at 1 μg/kg/h. The mean loading dose was 2.2 μg/kg with 52 patients requiring only the initial dose of 2 μg/kg. The time to achieve sedation ranged from 6 to 20 min. Sinus arrhythmias were noted in ten patients (16%). Heart rate and blood pressure decreased in all patients; however, no treatment was necessary and no hemodynamic value was less than the fifth percentile for age. No changes were observed in the $ETCO_2$ and no patient developed oxygen desaturation while breathing room air.

Given its limited analgesic effects, dexmedetomidine may not be the ideal agent when used alone for painful procedures. However, anecdotal experience suggests that a combination of dexmedetomidine with ketamine may be effective in such scenarios [309–312].

With the prolonged administration of any agent for sedation or analgesia, tolerance occurs and withdrawal may be seen if the medication is abruptly discontinued. Regardless of the agent or agents responsible, the potential role of dexmedetomidine in treating such problems is supported by animal studies [313–316], case reports in adults and children [317–321], and one retrospective case series in infants [322]. The latter study was a retrospective review of seven infants (3 to 24 months). Sedation had been provided during

mechanical ventilation with a continuous infusion of fentanyl supplemented with intermittent doses of midazolam. With discontinuation of the fentanyl and midazolam, withdrawal occurred. Dexmedetomidine was administered as a loading dose of 0.5 μg/kg/h followed by an infusion of 0.5 μg/kg/h. The loading dose was repeated and the infusion increased to 0.7 μg/kg/h in the two patients who had received the highest doses of fentanyl (8.5 ± 0.7 vs. 4.6 ± 0.5 μg/kg/h, $p < 0.0005$). Withdrawal was successfully controlled.

As with all of the medications discussed in this chapter, dexmedetomidine has been reported to effect cardiovascular function [302, 323–327]. Adverse hemodynamic effects include hypotension (mean arterial pressure ≤60 mmHg or a greater than 30% decrease from baseline) or bradycardia (heart rate ≤50 beats/min) [302]. Talke et al. evaluated the efficacy of dexmedetomidine infusion in a cohort of 41 adults during vascular surgery [324]. There was a lower heart rate, less tachycardia, and decreased norepinephrine levels during emergence from anesthesia in patients receiving dexmedetomidine.

Electrophysiologic effects were also reported in an intraoperative study by Peden et al. [325]. Two patients who received dexmedetomidine experienced brief episodes of sinus arrest following laryngoscopy and propofol administration. These findings suggest that specific procedures (laryngoscopy), techniques (hypothermia to control ICP or for neuroprotection), and medications (propofol, fentanyl, digoxin) may potentiate the vagotonic effects of dexmedetomidine.

Given these effects on cardiac conduction, it has been suggested that dexmedetomidine may not be a desirable agent for sedation in the cardiac catheterization suite when electrophysiologic studies are planned [326]. However, other authors have demonstrated that these negative chronotropic properties may be used as a therapeutic tool in infants and children who develop tachyarrhythmias following surgery for congenital heart disease [327].

Data in animal and human studies demonstrate beneficial effects on cerebral dynamics including a decrease in CBF and ICP [328, 329]. However, given the potential effects on mean arterial pressure, decreases in CPP may occur [330]. As with, the barbiturates, propofol and the inhalational anesthetic agents, animal data suggest that dexmedetomidine may provide some degree of cerebral protection during periods of global or regional cerebral ischemia [331–333]. The data in animal studies regarding its effects on the seizure threshold are mixed depending on the provocative agent and the type of animal studied, with two studies suggesting a lowering of the seizure threshold and two suggesting an anticonvulsant effect [334–337].

Chloral hydrate

Chloral hydrate, first synthesized in 1832, remains a commonly used agent for procedural sedation [338]. Its popularity results from several factors including its ease of administration by either oral or rectal route, healthcare providers' familiarity with it, and misconceptions regarding its margin of safety. Following oral or rectal administration, chloral hydrate is rapidly absorbed. It undergoes hepatic metabolism to its active metabolite, trichloroethanol (TCE). Although generally effective as a one-time agent for nonpainful radiologic procedures, repeated dosing in the PICU setting leads to excessive and prolonged CNS depression due to a variable half-life ranging from 9 to 40 h as well as the accumulation of active metabolites [339]. These issues have resulted in recommendations against such practices from the AAP [340].

Chloral hydrate is relatively contraindicated in neonates given its competition with bilirubin for protein binding sites. Additionally, the active metabolite, TCE, is related to the halogenated hydrocarbons and may cause ventricular arrhythmias especially in patients at risk for such problems (tricyclic antidepressant ingestions or underlying arrhythmia) [341, 342]. Given these issues, chloral hydrate has a limited role in sedation in the PICU setting; however, it may still have a place for sedation during nonpainful radiologic imaging [343]. Used for this purpose, doses of 75–100 mg/kg (maximum 2 g) can be administered by mouth or per rectum.

Tolerance, Physical Dependency, and Withdrawal

Over the past several years, data demonstrating the potential deleterious physiologic effects of untreated pain combined with ongoing humanitarian concerns have led to the increased use of sedative and analgesic agents. These initiatives have led to new consequences including physical dependency, tolerance, and withdrawal that require definition and effective treatment strategies. An appropriate place to begin the development of an effective approach to the patient with tolerance and physical dependency is a consensus on definitions of these terms [343]. Tolerance is a decrease in a drug's effect over time or the need to increase the dose to achieve the same effect. Tolerance is related to changes at or distal to the receptor, generally at the cellular level. Some authorities have divided tolerance into various subcategories including innate tolerance referring to a genetically predetermined lack of sensitivity to a drug, pharmacokinetic or dispositional tolerance referring to changes in a drug's effect because of alterations in distribution or metabolism, learned tolerance or a reduction in a drug's effect as a result of learned or compensatory mechanisms (learning to walk a straight line while intoxicated by repeated practice at the task), and pharmacodynamic tolerance [343]. With pharmacodynamic tolerance, although the plasma concentration of the drug remains constant, there is a decreased effect. For the purpose of this discussion, the latter phenomenon will be referred to as tolerance as the other issues are not as relevant when considering the PICU patient.

Withdrawal includes the physical signs and symptoms that manifest when the administration of a sedative or analgesic agent is abruptly discontinued in a patient who is physically tolerant. The symptomatology of withdrawal varies from patient to patient and may be affected by several factors including the agent involved, the patient's age, cognitive state, and associated medical conditions.

Physiologic (physical) dependence is the need to continue a sedative or analgesic agent to prevent withdrawal. Psychological dependence is the need for a substance because of its euphoric effects. Addiction is a complex pattern of behaviors characterized by the repetitive, compulsive use of a substance, antisocial or criminal behavior to obtain the drug, and a high incidence of relapse after treatment. Psychological dependency and addiction are extremely rare after the appropriate use of sedative or analgesic agents to treat pain or to relieve anxiety in the PICU setting.

The problems of opioid dependency and withdrawal in neonates and infants were first encountered in the 1970s and 1980s in infants of drug-addicted mothers [344–346]. Despite the difference in the origin of the problem, these studies provided valuable information for dealing with today's PICU population. The studies from the 1970s and 1980s have provided various pharmacologic treatment regimens as well as scoring systems that may be used to grade the severity of withdrawal and to evaluate the efficacy of the treatment regimens. Arnold et al. were among the first to recognize the problems of dependency and withdrawal after prolonged opioid administration in the PICU population [347].

In a retrospective review of 37 neonates who required extracorporeal membrane oxygenation (ECMO) for respiratory failure and who had received intravenous fentanyl for sedation, they sought to identify the signs and symptoms of the neonatal abstinence syndrome (NAS) and risk factors for its occurrence. Fentanyl infusion requirements to achieve the desired level of sedation increased from 11.6 ± 6.9 μg/kg/h on day 1 to 52.5 ± 19.4 μg/kg/h on day 8. By measuring plasma fentanyl levels, they were able to demonstrate that the tolerance was pharmacodynamic and not pharmacokinetic (related to increased metabolism of the opioid). NAS was related to the total fentanyl dose and the duration of the infusion. A cumulative fentanyl dose ≥1.6 mg/kg and an ECMO duration ≥5 days were risk factors for the development of NAS (odds ratio of 7 and 13.9, respectively).

In a cohort of eight infants placed on ECMO, fentanyl infusion requirements increased from 9.2 ± 1.9 μg/kg/h on day 1 to 21.9 ± 4.5 μg/kg/h on day 6 [348]. As in their previous study, they noted an increase in the plasma fentanyl concentration from 3.1 ± 1.1 ng/mL on day 1 to 13.9 ± 3.2 ng/mL on day 6.

Subsequent reports demonstrated withdrawal from other agents used for prolonged sedation in the PICU patient including benzodiazepines, barbiturates, propofol, and even the inhalational anesthetic agents. Sury et al. described benzodiazepine withdrawal in three children, who were 4, 11, and 12 years of age, after prolonged sedation with a continuous infusion of midazolam [350]. The patients had received midazolam for 7, 14, and 17 days at mean infusion rates of 0.17, 0.22, and 0.56 mg/kg/h. The midazolam infusions were stopped without tapering the infusion rate and within 24 h, withdrawal symptoms were noted including visual hallucinations, combative behavior, and seizures. The problems resolved once a benzodiazepine was administered.

Van Engelen et al. reported similar problems after the prolonged administration of midazolam to two pediatric patients [351]. The midazolam infusion rates reached maximum values of 0.14 and 0.57 mg/kg/h with durations of infusion of 12 and 29 days. After discontinuation of the midazolam infusion, both patients manifested withdrawal symptoms that included agitation, tachycardia, hyperpyrexia, and vomiting. Symptoms disappeared with reinstitution of the midazolam infusion.

Fonsmark et al. evaluated 40 children who received sedation during mechanical ventilation. Sedation was provided by midazolam, pentobarbital, or a combination of the two [352]. Withdrawal symptoms occurred in 14 of 40 patients (35%). A cumulative midazolam dose ≥60 mg/kg or a cumulative pentobarbital dose ≥25 mg/kg was associated with withdrawal, irrespective of the duration of infusion.

Other anecdotal reports have noted withdrawal following the use of pentobarbital for sedation in the PICU population [353]. The potential for the development of tolerance to barbiturates is further supported by animal studies demonstrating the rapid development of tolerance after repeated administration and an increased susceptibility to pentylenetetrazol-induced seizures as a manifestation of barbiturate withdrawal [354, 355].

Despite the concerns outlined above regarding propofol, it is still used for sedation during mechanical ventilation. In a retrospective review of acute withdrawal after prolonged sedation with propofol in the adult ICU patient, there was a correlation of the incidence of withdrawal behavior in patients with both the use of propofol as part of the sedation regimen and the dose administered [356]. Anecdotal evidence supports the occurrence of propofol withdrawal in a 10-month-old girl who required mechanical ventilatory support for 2 weeks after an inhalation smoke injury [357]. Propofol was administered for 2 weeks during mechanical ventilation. When the drug was discontinued, the patient exhibited "generalized twitching and jitteriness." No treatment was administered, and the symptoms subsided over a 3-day period.

One of the more novel approaches for sedation during mechanical ventilation is the administration of inhalational anesthetic agents, such as isoflurane. Arnold et al. reported their experience with the use of isoflurane to ten pediatric patients for sedation during mechanical ventilation (see above) [58]. During the administration of isoflurane, the opioid and benzodiazepine infusions were gradually tapered and discontinued. Although the inhalational agent proved effective in providing sedation, agitation and nonpurposeful movements occurred in 5 of the 10 patients within 2 h of discontinuation of isoflurane. These five patients had received more than 70 MAC-hours of isoflurane.

Arnold et al. subsequently reported tolerance and withdrawal phenomena after the prolonged administration of isoflurane to a 4-year-old boy for sedation during mechanical ventilation [358]. After 19 days of administration, with an end-tidal isoflurane concentration of 0.8–1.2%, the patient was awake and able to follow commands. After 32 days of administration, mechanical ventilation and the isoflurane were discontinued. Shortly after discontinuing the isoflurane, the patient developed agitation, diaphoresis, tachycardia, hypertension, and profuse diarrhea. The symptoms were eventually controlled with pentobarbital and midazolam infusions. Hughes et al. reported hallucinations and seizures after the prolonged administration of isoflurane for sedation to a 7-year-old boy [359].

Clinical signs and symptoms of withdrawal

The development of strategies to provide effective treatment of physical dependency and related problems requires the accurate identification and recognition of withdrawal symptoms. Ongoing or associated conditions that can manifest similar clinical signs and symptoms as withdrawal must be investigated and ruled out before concluding that the patient's symptoms are the result of withdrawal. In the PICU patient, these associated conditions may include central nervous system insults or infections, ICU psychosis, delirium, metabolic abnormalities, hypoxia, hypercarbia, and cerebral hypoperfusion from alterations in cardiac output or cerebral vascular disease.

Although many of the signs and symptoms of withdrawal are the same regardless of the agent, there may be subtle differences depending on the specific agent. The time to the onset of withdrawal symptoms varies depending on the half-life of the agent and the half-life of active metabolites, which may be several times longer than the parent compound. In general, the signs and symptoms of withdrawal from sedative and analgesic agents include signs and symptoms related to the CNS, the gastrointestinal tract, and the sympathetic nervous system. CNS manifestations are generally those of increased irritability including decreased sleep, tremulousness, hyperactive deep tendon reflexes, clonus, inability to concentrate, frequent yawning, sneezing, delirium, and hypertonicity. In neonates and infants, additional signs of central nervous system stimulation include a high-pitched cry and an exaggerated Moro reflex.

Seizures have been reported with withdrawal from opioids, benzodiazepines, barbiturates, propofol, and inhalational anesthetic agents while visual and auditory hallucinations have been described with opioid, benzodiazepine, barbiturate, and inhalational anesthetic withdrawal. GI manifestations including emesis, diarrhea, and feeding intolerance may be especially prominent in neonates and infants. When such problems occur in the absence of other signs and symptoms of withdrawal, they may be attributed to other problems and not withdrawal. Activation of the sympathetic nervous system with tachycardia, hypertension, dilated pupils, and tachypnea is a prominent finding with withdrawal from any of the above-mentioned sedative/analgesic agents. Additional signs and symptoms of sympathetic hyperactivity include nasal stuffiness, sweating, and fever.

Treatment of withdrawal and clinical scoring systems

As with most problems that arise in clinical medicine, effective treatment starts with prevention. Given that the incidence of withdrawal is related to the total amount of medication administered, careful titration of the sedative or analgesic agents using clinical sedation scales is optimal. There are currently no data to support or refute the efficacy of so-called drug holidays during the use of sedative and analgesic agents in the PICU setting. This practice involves turning off sedative and analgesic agents until the patient responds and then restarting the infusions at half of the previously used infusion rate. This practice effectively provides the same rationale as using clinical sedation scores in that excessive infusion rates are avoided. However, many physicians and certainly bedside nurses are hesitant to discontinue effective sedation and analgesia at times when painful processes may be present in the critically ill patient. Additionally, concerns have been raised that this practice may result in periods of excessive agitation in critically ill patients. Before such practices are universally embraced, prospective trials in the pediatric population are needed to demonstrate not only their efficacy but also their safety.

Prospective studies are needed to better address the efficacy of rotating sedation regimens, intermittent vs. continuous infusions of sedative/analgesic agents, and the role of other pharmacologic agents such as NMDA receptor antagonists and magnesium in preventing tolerance and dependency. Until further investigations provide additional insight into the factors controlling opioid dependency and ways of preventing or delaying

it, PICU physicians will be faced with a group of patients who require specific actions to prevent the development of withdrawal symptoms. Treatment strategies and protocols are necessary so that the problems associated with tolerance, physical dependency, and withdrawal do not limit the administration of these agents in the PICU population.

In order to provide effective therapy for patients with withdrawal, it may be helpful to identify those patients who are most likely to manifest symptoms of withdrawal and also to have scoring systems to identify and quantitate the signs and symptoms of withdrawal. As noted previously in this chapter, risk factors that have been identified include not only the total dose of the sedative or analgesic agent that has been administered but also the duration of the infusion.

In a prospective trial of 23 infants and children who had received fentanyl infusions for sedation during mechanical ventilation, Katz et al. determined the factors that could be used to identify the group who was at risk of withdrawal [360]: The total fentanyl dose and the duration of the infusion correlated with the risk of withdrawal, whereas the maximum fentanyl infusion rate did not. A total fentanyl dose ≥1.5 mg/kg or an infusion duration ≥5 days was associated with a 50% incidence of withdrawal, whereas a total fentanyl dose ≥2.5 mg/kg or an infusion duration ≥9 days was associated with a 100% incidence of withdrawal. Fonsmark et al. reported an increased probability of withdrawal in patients who received a total dose of midazolam ≥60 mg/kg or a total dose of pentobarbital ≥25 mg/kg [352].

Scoring systems may be helpful in the management of patients presenting with signs and symptoms of withdrawal, not only in identifying the behaviors or withdrawal but also in grading its severity and judging the response to therapy. Unfortunately, the majority of scoring systems were developed to deal with neonates born to drug-addicted mothers and therefore may not be applicable to the PICU population [361].

To address such issues, Ista et al. reviewed the literature regarding withdrawal scoring systems and found that of the six available in the literature, only two were directed toward the PICU population [362]. The first of these included the Sedation Withdrawal Score (SWS), which assigns points (0–2) to 12 withdrawal behaviors, thereby providing a maximum score of 24. The signs and symptoms are grouped to the CNS (tremor, irritability, hypertonicity, high pitched cry, convulsions, and hyperactivity), the GI system (vomiting and diarrhea), and the autonomic nervous system (fever, sweating, sneezing, and respiratory rate) [363]. The decision regarding weaning of the current sedative and analgesic regimen is based on the score (0–6 wean, 6–12 no change, 12–18 revert to previous regimen, more than 18 reevaluate plan). Ista et al. expressed concerns that this scale has not been validated in children and that in particular, there are no data regarding its sensitivity, specificity, validity, and reliability.

The other scale is the Opioid and Benzodiazepine Withdrawal Scale (OBWS) [364]. The OBWS is a 21-item checklist that evaluates 16 specific withdrawal behaviors. Franck et al. evaluated their scale by performing 693 assessments in 15 children who varied in age from 6 weeks to 28 months. Using 8 as a cut-off score for the presence of withdrawal, the sensitivity of the OBWS was only 50% with a specificity of 87%. The predictive value in terms of positive and negative ratios was 4.0 and 0.57 (considered moderate for a diagnostic tool) while the interrater reliability was acceptable at 0.8.

Because of these issues, Ista et al. concluded that a more appropriate scale was necessary in the PICU population and went on to use the data from their review to develop their own withdrawal scale [365]. Their withdrawal scale included all of the behaviors that had been reported in the literature as manifestations of withdrawal in the pediatric-aged patient. From this, they developed the Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC), which included 24 withdrawal symptoms. Over a 6-month period, they collected 2,188 observations in 79 children within 24 h of tapering off and discontinuing sedative and/or analgesic medication. They noted that specific symptoms including agitation, anxiety, muscle tension, sleeping for less than 1 h, diarrhea, fever, sweating, and tachypnea were observed most frequently

and that longer duration of opioid or benzodiazepine use and high doses were risk factors for withdrawal. Twenty-three observations were scored simultaneously and resulted in an inter-observer correlation coefficient of 0.85 with a range of 0.59–1.0 for the individual items.

By maintaining a high index of suspicion and the use of withdrawal scores developed for the PICU patient, it seems that we are closer to our goal of identifying patients who are manifesting withdrawal symptoms. As mentioned previously, the mainstay of preventing withdrawal must be the identification of high-risk patients and the slow weaning of sedative and analgesic agents. Withdrawal scales should still be applied to these patients in the event that withdrawal occurs despite our attempts to prevent it. Based on limited evidence-based medicine, it has been suggested that, in patients who have received sedative and analgesic infusions for more than 5–7 days, weaning can be accomplished at a rate of 10–20% per day [366, 367]. However, these studies have reported a significant incidence of withdrawal using these protocols thereby suggesting that a more reasonable approach may be a 5–10% decrease per day as has been suggested for adult patients and supported by some in the PICU population [368, 369].

When prolonged administration of opioids or other sedative agents will be necessary, switching to the oral administration of long-acting agents such as methadone may allow for earlier hospital discharge. This is especially true in patients who have received weeks of therapy and are on large doses of opioids and/or benzodiazepines. Advantages of methadone include its longer half-life allowing for dosing 2–3 times per day, an oral bioavailability of 75–90%, and availability as a liquid. Although the first report regarding the use of methadone suggested a starting dose of 0.1 mg/kg every 12 h, the three patients in the series were receiving relatively low opioid doses and, therefore, higher doses of methadone were not needed [349]. Clinical experience of this author has indicated that higher doses of methadone may be needed, depending on the dose of fentanyl. When considering the appropriate dose transition from intravenous fentanyl to oral methadone, consideration should be given to the differences in the potency and half-life of the two medications as well as cross-over tolerance [370]. Similar considerations are necessary when switching from intravenous midazolam to oral lorazepam.

Lugo et al. in a study evaluating enteral lorazepam to decrease midazolam requirements during mechanical ventilation suggested starting at a lorazepam dose that was 1/6th that of the total daily dose of intravenous midazolam [82]. Once the appropriate enteral/oral dose is determined and started, the intravenous administration is tapered off quickly.

After the initial reports regarding the use of methadone, other authors have suggested variations in conversion ratios from fentanyl to methadone as well as dosing intervals and most importantly weaning schedules [366, 367, 371–373]. Some have used intravenous methadone prior to oral methadone during the initial conversion process. Regardless of the protocol used, close observation during the conversion period is necessary to avoid adverse effects from oversedation or to recognize the early symptoms of withdrawal.

There remain some stigmata concerning the use of methadone. Therefore, a thorough discussion with the parents is necessary to discuss why methadone is being used and to outline the differences between addiction and physical dependency. Because of these issues as well as familiarity with long-acting morphine preparations, which are used in the treatment of children with chronic cancer-related pain, some physicians prefer to use the latter agent. However, these agents are available only in tablets that cannot be crushed so that administration and subsequent weaning protocols may be more difficult in younger patients. Methadone on the other hand is available in a liquid formulation. More recently, concern has been expressed for the adult who is on maintenance methadone for drug addiction regarding the potential for death, the potential for QT prolongation and arrhythmias [374]. To date, there are no such reports from the pediatric population; however, these concerns have led to the consideration of obtaining periodic ECG's

prior to and after instituting therapy with methadone.

A final issue with methadone is its metabolism by the P_{450} isoenzyme system of the liver making alterations in metabolism possible based on genetic factors and the coadministration of other medications. These factors should be considered when methadone is started or other medications are added to the patient's regimen.

In addition to opioids, nonopioid agents have been used to treat opioid withdrawal. In the author's opinion, this is less than optimal because it seems to make physiologic sense when dealing with the problems of tolerance and dependence to replace the missing agent rather than to treat the resulting symptoms. The benzodiazepine, diazepam, has been used to treat opioid withdrawal in neonates and infants [375].

When benzodiazepines are used to treat opioid-withdrawal in neonates born to drug-addicted mothers, clinical studies have demonstrated adverse effects on behavior including increased sedation and poor sucking as well as poor control of the autonomic hyperactivity that occurs with opioid withdrawal [376]. Similar results have been demonstrated with the use of phenobarbital [377, 378].

Phenothiazines (chlorpromazine) have also been used in the treatment of infants of drug-addicted mothers [379]. Despite relative success with an efficacy equivalent to that of phenobarbital, adverse effects including α-adrenergic blockade with hypotension and a lowering of the seizure threshold have limited their widespread application [380].

The centrally acting, α_2-adrenergic agonist, clonidine, has been used to treat and prevent opioid withdrawal in both neonates and adults [381–383]. Alpha$_2$-adrenergic receptors mediate part of their pharmacologic actions through the activation of the same potassium channel as opioid receptors. Because of its prolonged duration of action (12–18 h), once or twice a day dosing is possible. Starting doses range from 3 to 5 μg/kg/day.

Adverse effects from clonidine include sedation, bradycardia, and hypotension. Although the use of clonidine is becoming more widespread in pediatric anesthesia as a premedicant in the operating room as well as for caudal/epidural anesthesia; to date, there is limited clinical experience with its use in the treatment of opioid withdrawal.

Dexmedetomidine (Precedex®, Hospira Worldwide Inc, Lake Forest, IL) is the pharmacologically active dextro-isomer of medetomidine. Like clonidine, it exerts its physiological effects via α_2-adrenergic receptors. Regardless of the agent or agents responsible for withdrawal, the role of dexmedetomidine in treating such problems is supported by animal studies [313–316], case reports in adults and children [317–321], and one retrospective case series in infants [322].

The largest series reported in either the adult or pediatric population regarding the use of dexmedetomidine to control withdrawal is a retrospective review of seven infants ranging in age from 3 to 24 months [322]. The patients had received a continuous fentanyl infusion supplemented with intermittent doses of midazolam during mechanical ventilation. Withdrawal was documented and successfully treated with a bolus and subsequent infusion of dexmedetomidine. More recently, the feasibility of subcutaneous administration to treat or prevent withdrawal in infant and children has been demonstrated [384].

Delirium

In addition to the myriad of issues surrounding the provision or sedation and analgesia to critically ill patients, recent attention in clinical practice and in the literature, especially in the adult ICU population, has been focused on the issue of delirium following critical illnesses. In the ICU setting, delirium has been described as an acute and fluctuating disturbance of consciousness and cognition. In more general terms, the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) has defined delirium as a disturbance of consciousness and cognition that develops over a short period of time and fluctuates over time.

Over the years, several different terms and labels have been used to describe this syndrome in the ICU setting including ICU psychosis, ICU

syndrome, acute confusional state, encephalopathy, and acute brain failure. However, with a greater appreciation of the importance of this syndrome on the outcomes of critically ill patients and the need to appropriately identify it, the critical care community has recently conformed to the recommendations of the APA that the term "delirium" be used uniformly to describe this syndrome of brain dysfunction.

Delirium may occur in up to 80% of critically ill adults. Its short and long-term consequences include prolonged hospitalization as well as other morbidities. It may also be either a marker for or a direct cause of both short-term and long-term mortality risk of ICU patients [385, 386].

In a prospective evaluation meant to determine the immediate and long-term consequences of delirium in a cohort of 224 adult ICU patients, 183 (81.7%) developed delirium at some point during their ICU stay [387]. Demographics including age, comorbidity scores, dementia scores, activity of daily living scores, severity of illness, and admitting diagnosis were similar between those patients who developed delirium and those who did not. Patients who developed delirium had a higher 6-month mortality rate (34 vs. 15%, $p=0.03$) and spent 10 days longer in the hospital than those patients who did not develop delirium ($p<0.001$). Additional morbidities related to delirium included prolonged ICU stay, prolonged duration of requirements for mechanical ventilation, and increased costs of care following hospital discharge [385–388].

Classification of delirium

Given difficulties with identification, even in the adult population, delirium may often go unrecognized or attributed to other diseases processes or comorbid conditions such as dementia and depression or considered a natural, acceptable complication of a critical illness. Delirium can generally be divided into hypoactive and hyperactive subtypes, which outside of the ICU population have been shown to have some prognostic values. Hypoactive delirium, which tends to account for the majority of cases in the ICU setting, is characterized by decreased responsiveness, withdrawal behaviors, apathy, and depression. Hyperactive delirium, as the name implies, is characterized by agitation, restlessness, and emotional lability [389].

In a prospective evaluation of delirium in a cohort of adult medical ICU patients, Peterson et al. reported that purely hyperactive delirium was uncommon, occurring in 1.6% of the patients, hypoactive delirium occurred in 43.5% of the patients while 54.1% had mixed delirium [390]. Ouimet et al. proposed an alternative scheme for the categorization of delirium in the ICU setting, which is based on the number of symptoms of delirium that are present [391]. Six hundred ICU patients were observed for symptoms of delirium and then categorized according to the number of symptoms present. No delirium was present if there were no symptoms, patients with four or more symptoms were classified as having "clinical delirium" while an intermediate state which the authors termed "subsyndromal delirium" was thought to be present in patients who manifested 1–3 symptoms.

Diagnosis of delirium

Given its impact on short and long-term outcome in the ICU patient, the accurate diagnosis of delirium is mandatory to identify its occurrence following critical illness and to facilitate trials to determine ways to limit its occurrence. As noted previously, the underdiagnosis and recognition of delirium remain a significant problem [392]. Such issues have led to the suggestion by the Society for Critical Care Medicine that some type of delirium screening tool should be used in all critically ill patients. As with depth of sedation and withdrawal, there are instruments which have been validated for the assessment of delirium in ICU patients. To date, these instruments have only been studied in the adult population. Two such tools are (1) the Intensive Care Delirium Screening Checklist (ICDSC) and the (2) Confusion Assessment Method for the ICU (CAM-ICU) [393, 394] (Table 13.4). The scoring systems allow the

Table 13.4 The intensive care delirium screening checklist

Patient evaluation	Day 1	Day 2	Day 3	Day 4	Day 5
Altered level of consciousness* (A–E)					
If A or B do not complete patient evaluation for the period					
Inattention					
Disorientation					
Hallucination—delusion—psychosis					
Psychomotor agitation or retardation					
Inappropriate speech or mood					
Sleep/wake cycle disturbance					
Symptom fluctuation					
Total score (0–8)					

* Level of consciousness:
A: No response, score: None
B: Response to intense and repeated stimulation (loud voice and pain), score: None
C: Response to mild or moderate stimulation, score: 1
D: Normal wakefulness, score: 0
E: Exaggerated response to normal stimulation, score: 1
(reproduced from Bergeron et al. [393], with permission from Springer)

assessment and diagnosis of delirium in ICU patients by nonpsychiatric-trained physicians and healthcare workers in the ICU. These tools can be used even in patients who are unable to speak because of the presence of an ETT.

Both scoring tools begin with an assessment of the patient's responsiveness and no further evaluation is undertaken if the patient is obtunded or deeply sedated. The ICDSC rates the level of consciousness from A to E, with A denoting no response and E denoting exaggerated response to normal stimulation. If an A (no response) or B (response to intense or repeated stimulation) is obtained, no further assessment is undertaken. For patients who manifest a C, D, or E level, a further evaluation for the presence of delirium is undertaken. This includes assessing inattentiveness, disorientation, hallucination-delusional-psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep–wake cycle disturbances, and symptom fluctuation. These seven checklist items are added to altered level of consciousness to give eight possible items which are scored as present or absent to give a total delirium score of 0–8 with four or more considered diagnostic of delirium.

Risk factors for the development of delirium

As with many outcomes in the ICU, the risk factors for the development of delirium include factors that may be present prior to the onset of the acute illness and those that relate directly to the acute illness or medications administered during it. Patient comorbidities that may increase the likelihood of delirium include advanced age, hypertension, the severity of illness, history of tobacco use, and baseline cognitive impairment. Other potential risk factors include metabolic disturbances (plasma levels of sodium, calcium, and blood urea nitrogen), acute infection, respiratory disease, acidosis, anemia, and hypotension. Additionally, there may be some genetic predisposition to the development of delirium.

Ely et al. evaluated the possible association of the apolipoprotein E genotype and delirium among 53 mechanically ventilated medical ICU patients [395]. Patients with the apolipoprotein-4 polymorphism (a risk factor for Alzheimer's disease) manifested delirium twice as long as those without this polymorphism. The duration of delirium (median and interquartile range) was 4 days (3–4.5 days) vs. 2 days (1–4 days, $p = 0.05$).

Also of significant concern in the ICU patient is the potential association between delirium and medications used for sedation or analgesia. To date, the most compelling evidence suggests that medications which act through the GABA system increase the likelihood of delirium. Most notable of the GABA-agonists in the role of delirium are the benzodiazepines including both midazolam and lorazepam [396].

There are little or no data to demonstrate any relationship between the use of opioids such as morphine or fentanyl and the risk of developing delirium. Rather, the appropriate use of opioids for analgesia may decrease its incidence: Ouimet et al. reported that the mean daily dose of opioid dose was higher among patients without delirium than among those with delirium [397]. Similarly, in a cohort of 541 adult patients who were hospitalized for a hip fracture, those who received more than 10 mg/day of parenteral morphine or morphine-equivalents were less likely to develop delirium than patients who received less analgesia [398]. Treatment with meperidine was an exception as meperidine has been shown to increase the risk of delirium when compared with other opioids.

Pathophysiology of delirium

The exact cellular or physiologic mechanisms of delirium remain poorly defined. Additionally, it is likely that it may result from a multifactorial process, resulting from a combination of underlying patient factors, the critical illness, and medications used in the ICU setting. One theory that has been supported by clinical research is that delirium results from a neurotransmitter imbalance. Derangements of several different central neurotransmitters have been theorized to result in delirium, although the greatest focus has been on alterations in the central concentrations of dopamine and acetylcholine [399, 400]. Specifically, an excess of dopamine or relative deficiencies in acetylcholine may result in delirium. Other potential central neurotransmitters which may play a role in the pathogenesis of delirium include GABA, serotonin, endorphins, and glutamate [401, 402]. Other evidence has pointed toward inflammation as a potential etiologic factor in the development of delirium. Animal studies have demonstrated that an inflammatory cascade may result in alterations in the blood–brain barrier, changes in vascular permeability within the CNS, and EEG changes consistent with those seen in ICU patients who develop delirium [403]. The end result of this inflammatory process may provoke delirium through alterations in CBF, by interfering with normal neurotransmitter function, or altering neurotransmitter concentrations within the CNS.

Prevention and treatment of delirium

Given the prevalence and adverse effects of delirium in the ICU setting, appropriate interventions include not only treatment once delirium has occurred but also potentially strategies to limit its incidence. Although performed in a non-ICU population, Inouye et al. nonrandomly assigned 852 hospitalized elderly patients to usual care or management with a multiple component strategy aimed at decreasing the incidence of delirium [404]. The interventions included repeated reorientation of the patient, the provision of cognitively stimulating activities, a nonpharmacologic protocol to improve sleep, ambulation and mobilization activities, range of motion exercises, timely removal of catheters and physical restraints, and improvement in sensory input through the use of eyeglasses, magnifying lenses, and hearing aids. These interventions significantly reduced the incidence of delirium (15.0% in the standard care group vs. 9.9% in the intervention group). Given the outcome of this and other similar trials, such protocols have been recommended for use in the ICU. It must also be recognized that the use of sedative medications increases the incidence of delirium and efforts should be made to minimize dosages [405].

Haloperidol has been recommended as the drug of choice for the treatment of ICU delirium by both the Society of Critical Care Medicine and the APA. Classified as a typical antipsychotic, haloperidol blocks dopamine$_2$ receptors thereby

decreasing agitation, hallucinations, and delusions. Given the lack of prospective, clinical trials, the optimal dose regimen has not been defined. Recommendations from the Society of Critical Care Medicine for adults include an initial dose of 2 mg intravenously, followed by repeated doses (doubling the previous dose) every 15–20 min until the agitation is controlled. Once the agitation subsides, scheduled doses (every 4–6 h) are recommended for 2–3 days followed by a tapering of the dose once the problem has resolved. In addition to its use as treatment for acute delirium, haloperidol has been shown to be effective when used as a prophylactic agent to prevent delirium in a cohort of elderly patients [406]. The atypical antipsychotics (risperidone, ziprasidone, quetiapine, and olanzapine) may also be helpful in the treatment of delirium, but only preliminary data exist supporting their use in the ICU [407].

Patients treated with haloperidol or other antipsychotics should be monitored for adverse effects including cardiac arrhythmias due to effects on repolarization (these effects are less common with the atypical antipsychotic agents), hypotension, dystonic reactions, extrapyramidal effects, malignant neuroleptic syndrome, and lowering of the seizure threshold. Given the potential for the development of lethal cardiac arrhythmias including torsades de pointes, these agents are contraindicated in patients with a prolonged QT interval. Anticholinergic effects such as dry mouth, constipation, and urinary retention may also occur.

Summary

A cookbook approach to sedation and analgesia in the PICU is not feasible due to the wide variation in patients, ages, comorbid diseases, and clinical scenarios faced in this population. As no single agent will be effective in all patients and all scenarios, healthcare providers must be facile with the use of a wide array of sedative and analgesic agents. The three primary choices that must be made when choosing a sedative/analgesic agent are the agent, its route or delivery, and the mode of delivery.

In most scenarios, sedation during mechanical ventilation is initiated with either a benzodiazepine or an opioid. There is an abundance of clinical experience with midazolam in the PICU population although lorazepam may provide an effective alternative with a longer half-life and more predictable pharmacokinetics without the concern of active metabolites. However, there are limited reports regarding its use in the PICU population and there may be concerns regarding accumulation of the diluent, propylene glycol.

Although fentanyl is frequently chosen because of its hemodynamic stability and beneficial effects on PVR, morphine is an effective alternative with data to suggest that the development of tolerance may be slower and that there may be fewer issues with withdrawal when compared to fentanyl. Long-term follow-up studies have demonstrated no adverse CNS developmental effects from morphine use in neonates and infants. In the critically ill infant at risk for pulmonary hypertension, the literature continues to support the use of the synthetic opioids given their ability to modulate PVR and prevent pulmonary hypertensive crisis. When these agents fail or lead to adverse effects, alternatives include ketamine, pentobarbital, or dexmedetomidine.

Ketamine may be useful for the patient with hemodynamic instability or with increased airway reactivity as a component of their disease process. To date, there are limited reports regarding the use of pentobarbital in the PICU with recent concerns being raised regarding a high incidence of adverse effects associated with its use. Propofol has gained great favor in the adult population as a means of providing deep sedation while allowing for rapid awakening. Similar beneficial properties are achieved in the pediatric-aged patient; however, concerns of the propofol infusion syndrome have significantly limited its use in the PICU population. As the pediatric experience increases, it appears that there will be a role for newer agents such as dexmedetomidine. The use of dexmedetomidine may continue to increase as the incidence of delirium has been shown to be less with its use when compared to commonly used benzodiazepines [408]. Suggested starting guidelines for sedative and analgesic agents are outlined in Table 13.3.

The second decision regarding PICU sedation includes the mode of administration. Effective sedation and analgesia are generally most easily achieved with the use a continuous infusion of a benzodiazepine or opioid supplemented with as needed bolus doses to provide additional analgesia or sedation. These bolus doses are given during periods of breakthrough agitation or prior to noxious stimulation such as tracheal suctioning or other nursing interventions. Patients requiring frequent bolus doses should have the baseline infusion rate increased. As the infusion rate is increased, the bolus doses should be increased to equal the hourly rate. The titration of the infusion and use of supplemental bolus doses should be adjusted using clinical sedation scales.

The third decision regarding sedative and analgesic agents is the route of administration. In the PICU setting, the intravenous route is used in the vast majority of patients. However, specific circumstances may exist which necessitate the use of a nonintravenous route. Although medications such as midazolam have been administered via many nonparenteral routes including oral and transmucosal administration, these routes will have a limited role in the PICU population although they are viable options for procedural sedation. The subcutaneous route may be used in specific circumstances while future clinical trials with inhalational anesthetic agents may provide us with more information regarding these agents in infants and children.

When sedative and analgesic agents are administered, adverse effects on physiologic function may follow [341]. Monitoring of the patient's physiologic function is mandatory whenever these agents are in use. There is also an increased understanding and recognition of withdrawal syndromes which may occur following the prolonged administration of sedative and analgesic agents. Strategies are needed to identify those patients at risk for withdrawal followed by appropriate interventions to prevent or treat it. With these caveats in mind, the goal of providing effective and safe sedation and analgesia for all of our patients is within reach.

Case Studies

Case 1

A 10-year-old, 48 kg boy is brought to the emergency room following a motor vehicle accident. His injuries included a closed head injury and a right femur fracture. A computed tomography scan is requested to rule out intra-abdominal injuries. His vital signs are stable and his Glasgow Coma Scale is 11. His neck is stabilized in a hard cervical collat. He is sleepy, but has intermittent periods of combative behavior. Sedation is requested for the CT imaging.

***Considerations*:** This patient's altered mental status and potential for a full-stomach make sedation without control of the airway potentially problematic in that loss of airway reflexes may result in upper airway obstruction, the need for bag-valve-mask ventilation with the risks of aspiration. Given these concerns, the decision is made not to provide with sedation, but rather to protect the airway with endotracheal intubation and induce general anesthesia. Given the potential for associated injuries which may result in blood loss and decreased intravascular volume, etomidate is chosen for the induction of general anesthesia.

***Drugs*:** Etomidate (Amidate, Abbott Pharmaceuticals) is an intravenous anesthetic agent, introduced into clinical practice in 1972, whose primary effects of sedation and amnesia are mediated through the GABA inhibitory neurotransmitter system. Following intravenous administration, loss of consciousness is rapid (15–20 s) and as with propofol and the barbiturates, its duration of action following a single bolus dose is related

to redistribution rather than metabolism and clearance. Beneficial CNS effects include a decrease of the $CMRO_2$, CBF, and ICP. CPP is maintained because of minimal effects on myocardial function. Although the barbiturates and propofol have similar effects on CHS dynamics, the latter agents are likely to decrease MAP and thereby decrease CPP. Myoclonic movements are also a frequently observed effect following the rapid intravenous administration of etomidate. Although these movements may simulate tonic-clonic seizure activity, no epileptiform discharges are noted. It has been suggested that the myoclonic movements are of spinal origin resulting from disinhibition of inhibitory neuronal pathways. Pretreatment with fentanyl, benzodiazepines, or a small dose of etomidate has been shown to be effective in decreasing the incidence of myoclonus. The most significant concern with etomidate and the factor that limits its long-term administration in the ICU setting is its effects on the endogenous production of corticosteroids. This effect was identified when an increased risk of mortality was noted in adult ICU patients who were sedated with a continuous infusion of etomidate. Etomidate inhibits the enzyme, 11-b hydroxylase, which is necessary for the production of cortisol, aldosterone, and corticosterone. To date, significant controversy surrounds the clinical significance of the adrenal suppression following a single induction dose of etomidate with some authors calling for the abandonment or at least a reevaluation of the use of etomidate. The duration of the adrenal suppression produced by a single induction dose of etomidate has varied from study to study, but may exceed 12 h. However, no study has demonstrated changes in clinical outcome based on the adrenal suppression following a single dose of etomidate. Therefore, no definite decision can be reached regarding whether the use of etomidate should be eliminated from clinical practice and even in the scenario presented, its use may be considered somewhat controversial. Given its effects on cerebral dynamics, it also should be considered for patients with increased ICP with or without associated myocardial dysfunction. A rapid sequence intubation is performed with manual in-line stabilization following the administration of etomidate and succinylcholine. This is followed by a propofol infusion starting at 25 mg/kg/min and titrated up based on the hemodynamic response to allow for completion of the CT scan. Following this, the patient is admitted to the Pediatric ICU and his trachea is extubated once his mental status has returned to baseline.

Case 2

A 26-month-old infant is recovering from surgery for congenital heart disease. Following the surgical procedure, the infant is sedated with a fentanyl infusion with intermittent doses of midazolam for 4 days during mechanical ventilation. In anticipation of extubation, the fentanyl which was infusing at 8 μg/kg/min and the intermittent doses of midazolam are discontinued. Three hours later, the infant is tachycardic, hypertensive, has dilated pupils, and a temperature of 38.6°C.

***Considerations*:** This infant is likely manifesting signs and symptoms of withdrawal; however, other possibilities must be excluded as the diagnosis of withdrawal is a diagnosis of exclusion. The work-up would include a thorough physical examination and perhaps laboratory evaluation including a complete blood count and blood gas analysis to rule out hypercarbia, hypoxemia, decreased cardiac output, and infection. Although this patient falls below the 50% incidence of withdrawal given that the infusion was continued for only 4 days, withdrawal may still occur in this patient. Some type of withdrawal scale that is specific for the Pediatric ICU patient may help to identify the severity of the withdrawal as well as the

response to therapy. The OBWS is a 21-item checklist that evaluates 16 specific withdrawal behaviors. The patient scores a 12 indicative of withdrawal. Given the brief duration of the fentanyl infusion, it is decided that weaning may be accomplished relatively rapidly without affecting the duration of the PICU stay. Therefore, the decision is made to reinstitute intravenous therapy.

***Drugs*:** Given that this patient is extubated and breathing spontaneously, it is decided to use dexmedetomidine which may have less effect on ventilatory function than opioids or benzodiazepines. Dexmedetomidine is the pharmacologically active dextro-isomer of medetomidine. Like clonidine, it exerts its physiological effects via α2-adrenergic receptors. Dexmedetomidine and clonidine are members of the imidazole subclass which exhibits a high ratio of specificity for the α2 vs. the α1 receptor. However, while clonidine exhibits an α2:α1 specificity ratio of 200:1, that of dexmedetomidine is 1,600:1 thereby making it a complete agonist at the α2-adrenergic receptor. Dexmedetomidine has a short half-life (2–3 vs. 12–24 h for clonidine) and is commercially available for intravenous administration. Adverse effects are generally limited with dexmedetomidine although hemodynamic effects (bradycardia or hypotension) may occasionally be seen. As with clonidine, there is increasing experience and interest regarding the use of dexmedetomidine in the prevention and treatment of withdrawal following the prolonged administration of opioids and benzodiazepines in the PICU setting. Regardless of the agent or agents responsible for withdrawal, the role of dexmedetomidine in treating such problems is supported by animal studies, case reports in adults and children, and one retrospective case series in infants. A loading dose of dexmedetomidine (0.5 μg/kg) was administered over 10 min followed by an infusion of 0.5 μg/kg/h. Ongoing OBWS values decreased to 1–3 over the ensuring 3–4 h. The dexmedetomidine was decreased in increments of 0.1 μg/kg/h with constant observation of the OBWS. Alternatively, dexmedetomidine can also be administered subcutaneously if there is a need to remove central lines and eliminate the need for vascular access.

Case 3

A 10-month-old infant is admitted to the PICU following direct laryngoscopy and airway laser in the operating room. Direct laryngoscopy revealed a subglottic hemangioma which was effectively treated with the laser and the patient remains intubated with a 4.0 ETT given concerns of edema and airway swelling. The otolaryngologist requests overnight sedation (16–18 h) to ensure that the airway edema has resolved and that the trachea can be successfully extubated. On arrival in the PICU, the infant is initially comfortable with a Ramsay sedation score of 4. Sedation is initiated with morphine at 30 μg/kg/h and midazolam at 0.5 mg/kg/h. The patient gradually becomes more awake and then agitated with Ramsay scores of 1. Four bolus doses of midazolam (0.1 mg/kg) and two of morphine (0.05 mg/kg) are given and the morphine infusion is increased to 50 and then to 100 μg/kg/hr while the midazolam infusion is increased to 0.25 mg/kg/h. Four hours later, the patient's Ramsay scores are 1–2 again.

***Considerations*:** The goals of sedation in this patient are to maintain a deep level of sedation and then rapid awakening to ensure full respiratory function and upper airway control prior to endotracheal intubation. In a small subset of patients, the usual combination of an opioid (morphine or fentanyl) and midazolam fails to provide the needed depth of sedation. An additional concern with this combination is that these agents demonstrated a context-sensitive half-life whereby prolonged awakening may occur following a brief-duration infusion of more than 12–24 h.

***Drugs*:** There are a couple of options for this patient including the use of potent inhalational anesthetic agents, propofol or remifentanil. To date, there remain limited data regarding the use of the potent inhalational anesthetic agents for sedation in the PICU setting. A benefit of these agents is the ability to rapidly control the depth of anesthesia as well as rapid awakening upon their discontinuation. These agents may have some effect on hemodynamic function, but are generally well tolerated in patients without comorbid cardiac diseases of hypovolemia. The major obstacles to the use of the inhalational anesthetics in the PICU patient are issues with administration, monitoring, scavenging, and environmental pollution. Although techniques are available to allow the administration of these agents through ICU ventilators, the added cost and logistic issues limit their use. Given the problems with the devices and techniques currently available for the delivery of the potent inhalational anesthetic agents in the ICU setting, novel means of delivering these agents are needed. The Anesthetic Conserving Device or "AnaConDa®" is a modified heat-moisture exchanger with a deadspace of 100 mL which may allow a simplified means of administering the potent inhalational anesthetic agents in the ICU setting. The device is placed between the Y-piece of the ventilator circuit and the 15 mm adaptor of the ETT. There is also a port at the end of the device just proximal to its attachment to the ETT which allows gas sampling and monitoring of the agent concentration. The desired inspired concentration is titrated by adjusting the infusion rate on the syringe pump based on the manufacturer's recommendations. Exhaled isoflurane is adsorbed to the lipophilic carbon particle filter in the device and redelivered to the patient thereby limiting environmental pollution.

Another option would be the short-term infusion of propofol. Propofol is an alkyl phenol compound (2,6-diisopropylphenol) with general anesthetic properties. Although its chemical structure is distinct from that of other intravenous anesthetic, its mechanism of action is similar as it acts through the GABA system [170]. Although propofol was initially introduced into anesthesia practice for the induction and maintenance of anesthesia, its rapid onset and recovery times led to its eventual use for sedation in the ICU setting. When compared with midazolam for sedation in adult patients, propofol has been shown to provide shorter recovery times, improved titration efficiency, reduced post-hypnotic obtundation, and faster weaning from mechanical ventilation with limitation of issues surrounding context-sensitive half-life. Despite its potential benefits in the ICU setting and its efficacy for providing sedation during mechanical ventilation, the routine use of propofol is not recommended and, in fact, is considered contraindicated by many authorities because of the potential for the development of what has been termed the "propofol infusion syndrome." First described in 1992, the disorder includes metabolic acidosis, bradycardia, dysrhythmias, rhabdomyolysis, and fatal cardiac failure. Given these concerns, the manufacturer of propofol has cautioned against its use in the PICU patient. In specific clinical scenarios, propofol is still used as a short term drug (6–12 h) to transition from other agents such as fentanyl and midazolam to allow for more rapid awakening when we are ready for tracheal extubation. In these cases, intermittent monitoring of acid–base status is suggested with discontinuation of the propofol infusion should acidosis develop.

The final option is remifentanil. Remifentanil is a synthetic opioid that is metabolized by nonspecific esterases in the plasma. It has a clinical half-life of 5–10 min and a brief duration of effect even following 12–24 h of continuous infusion. These pharmacokinetic parameters hold true even in the neonatal population, making remifentanil the only opioid whose pharmacokinetics is not altered by gestational or chronologic age. Given these

properties, it is a potentially useful agent for providing a deep level of sedation and yet allowing for rapid awakening with discontinuation of the infusion even in the neonatal population. Although there is significant clinical experience with the use of remifentanil during surgical procedures in patients of all ages; to date, there are only anecdotal reports regarding its use in the PICU population. However, these reports demonstrate rapid control of the depth of anesthesia and rapid awakening when the infusion is discontinued. Unlike other opioids, remifentanil does not demonstrate a context-sensitive half-life and its duration of action remains constant even with a prolonged issue. Issues include the rapid development of tolerance, limiting its efficacy for more than 24 h as well as cost.

Remifentanil is chosen to provide sedation. An infusion is started at 0.2 μg/kg/min and the morphine infusion is discontinued after 15 min. The remifentanil is increased to 0.3 μg/kg/min and the midazolam infusion is incrementally decreased and discontinued after 2 h. Over the next 12 h, the Ramsay scores are 4–5 and the infusion is increased to 0.4 μg/kg/min. The next morning, an airleak is present around the ETT and upper airway examination in the PICU reveals no concerns of airway edema. The remifentanil infusion is discontinued and 15 min later, the patient's trachea is extubated without difficulty.

References

1. Mendelsohn AB, Belle SH, Fischhoff B, et al. How patients feel about prolonged mechanical ventilation 1 yr later. Crit Care Med. 2002;30:1439–45.
2. Malviya S, Voepel-Lewis T, Tait AR. Adverse events and risk factors associated with the sedation of children by non-anesthesiologists. Anesth Analg. 1997;85:1207–13.
3. Practice Guidelines for Sedation and Analgesia by Non-anesthesiologists. A report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Anesthesiology. 1996;84:459–71.
4. Keidan I, Gozal D, Minuskin T, et al. The effect of fasting practice on sedation with chloral hydrate. Pediatr Emerg Care. 2004;20:805–7.
5. Treston G. Prolonged pre-procedure fasting time is unnecessary when using titrated intravenous ketamine for paediatric procedural sedation. Emerg Med Australas. 2004;16:145–50.
6. Mace SE, Brown LA, Francis L, et al. Clinical policy: critical issues in the sedation of pediatric patients in the emergency department. Ann Emerg Med. 2008;51:378–99.
7. American Academy of Pediatrics and the American Academy of Pediatric Dentistry Work Group on Sedation. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Pediatrics. 2006;118:2587–602.
8. Cote CJ, Notterman DA, Karl HW, et al. Adverse sedation events in pediatrics: a critical incident analysis of contributing factors. Pediatrics. 2000;105:805–14.
9. Hart LS, Berns SD, Houck CS, et al. The value of end-tidal CO2 monitoring when comparing three methods of conscious sedation for children undergoing painful procedures in the emergency department. Pediatr Emerg Care. 1997;13:189–93.
10. Tobias JD. End-tidal carbon dioxide monitoring during sedation with a combination of midazolam and ketamine for children undergoing painful, invasive procedures. Pediatr Emerg Care. 1999;15:173–5.
11. Ambuel B, Hamlett KW, Marx CM, Blumer JL. Assessing distress in pediatric intensive care environments: the COMFORT scale. J Pediatr Psychol. 1992;17:95–109.
12. Crain N, Slonim A, Pollack MM. Assessing sedation in the pediatric intensive care by using BIS and COMFORT scale. Pediatr Crit Care Med. 2002;3:11–4.
13. Ista E, van Dijk M, Tibboel D, de Hoog M. Assessment of sedation levels in pediatric intensive care unit patients can be improved by using the COMFORT "behavior" scale. Pediatr Crit Care Med. 2005;6:58–63.
14. Simmons LE, Riker RR, Prato BS, Fraser GL. Assessing sedation during intensive care unit mechanical ventilation with the bispectral index and sedation-agitation scale. Crit Care Med. 1999;27:1499–504.
15. Ramsay M, Savage TM, Simpson ER, et al. Controlled sedation with aphalaxone-alphadone. BMJ. 1974;2:656–9.
16. Hartwig S, Roth B, Theisohn M. Clinical experience with continuous intravenous sedation using midazolam and fentanyl in the paediatric intensive care unit. Eur J Pediatr. 1991;150:784–8.

17. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol. 1992;12:43–8.
18. Macnab AJ, Levine M, Glick N, et al. A research tool for measurement of recovery from sedation: the Vancouver Sedative Recovery Scale. J Pediatr Surg. 1991;26:1263–7.
19. Malviya S, Voepel-Lewis T, Tait AR, et al. Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS). Br J Anaesth. 2002;88:241–5.
20. Flaishon RI, Windsor A, Sigl J, Sebel PS. Recovery of consciousness after thiopental or propofol. Bispectral index and isolated forearm technique. Anesthesiology. 1997;86:613–9.
21. Sebel PS, Lang E, Rampil IJ, White PF, Cork R, Jopling M, et al. A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. Anesth Analg. 1997;84:891–9.
22. Gill M, Green SM, Krauss B. A study of the bispectral index monitor during procedural sedation and analgesia in the emergency department. Ann Emerg Med. 2003;41:234–41.
23. Brown McDermott N, VanSickle T, Motas D, Friesen RH. Validation of the bispectral index monitor during conscious and deep sedation in children. Anesth Analg. 2003;97:39–43.
24. Motas D, Brown McDermott N, VanSickle T, Friesen RH. Depth of consciousness and deep sedation attained in children as administered by nonanesthesiologists in a children's hospital. Pediatr Anesth. 2004;14:256–9.
25. Berkenbosch JW, Fichter CR, Tobias JD. The correlation of the bispectral index monitor with clinical sedation scores during mechanical ventilation in the pediatric intensive care unit. Anesth Analg. 2002;94:506–11.
26. De Deyne C, Struys M, Decruyenaere J, Creupelandt J, Hoste E, Colardyn F. Use of continuous bispectral EEG monitoring to assess depth of sedation in ICU patients. Intensive Care Med. 1998;24:1294–8.
27. Aneja R, Heard AMB, Fletcher JE, Heard CMB. Sedation monitoring of children by the bispectral index in the pediatric intensive care unit. Pediatr Crit Care Med. 2003;4:60–4.
28. Arbour RB. Using the bispectral index to assess arousal response in a patient with neuromuscular blockade. Am J Crit Care. 2000;9:383–7.
29. Courtman SP, Wardugh A, Petros AJ. Comparison of the bispectral index monitor with the COMFORT score in assessing level of sedation of critically ill children. Intensive Care Med. 2003;29:2239–46.
30. Vivien B, Di Maria S, Ouattara A, Langeron O, Coirat P, Riou B. Overestimation of bispectral index in sedative intensive care unit patients revealed by administration of muscle relaxant. Anesthesiology. 2003;99:9–17.
31. Messner M, Beese U, Romstock J, Dinkel M, Tschaikowsky K. The bispectral index declines during neuromuscular blockade in fully awake persons. Anesth Analg. 2003;97:488–91.
32. Goto T, Nakata Y, Saito H, et al. Bispectral analysis of the electroencephalogram does not predict responsiveness to verbal command in patients emerging from xenon anesthesia. Br J Anaesth. 2000;85:359–63.
33. Barr G, Jakobsson G, Owall A, Anderson RE. Nitrous oxide does not alter bispectral index: study with nitrous oxide as sole agent and as an adjunct to IV anaesthesia. Br J Anaesth. 1999;82:827–30.
34. Lallemand MA, Lentschener C, Mazoit JX, Bonnichon P, Manceau I, Ozier Y. Bispectral index changes following etomidate induction of general anaesthesia and orotracheal intubation. Br J Anaesth. 2003;91:341–6.
35. Tobias JD, Grindstaff R. Bispectral index monitoring during the administration of neuromuscular blocking agents in the pediatric ICU patient. J Intensive Care Med. 2005;20:233–7.
36. Grindstaff R, Tobias JD. Applications of bispectral index monitoring in the pediatric intensive care unit. J Intensive Care Med. 2004;19:111–6.
37. Tobias JD. Monitoring the depth of sedation in the pediatric ICU patient: where are we, or more importantly, where are our patients. Pediatr Crit Care Med. 2005;6:715–8.
38. Tobias JD, Berkenbosch JW. Tolerance during sedation in a pediatric ICU patient: effects on the BIS monitor. J Clin Anesth. 2001;13:122–4.
39. Volles DF, McGory R. Pharmacokinetic considerations. Crit Care Clin. 1999;15:55–7.
40. Buck ML, Blumer JL. Opioids and other analgesics: adverse effects in the intensive care unit. Crit Care Clin. 1991;7:615–37.
41. Reed MD, Blumer JL. Therapeutic drug monitoring in the pediatric intensive care unit. Pediatr Clin North Am. 1994;41:1227–43.
42. de Wildt SN, de Hoog M, Vinks AA, van der Giesen E, van den Anker JN. Population pharmacokinetics and metabolism of midazolam in pediatric intensive care patients. Crit Care Med. 2003;31:1952–8.
43. Chua MV, Tsueda K, Doufas AG. Midazolam causes less sedation in volunteers with red hair. Can J Anaesth. 2004;51:25–30.
44. Katz R, Kelly HW. Pharmacokinetics of continuous infusions of fentanyl in critically ill children. Crit Care Med. 1993;21:995–1000.
45. De Jonghe B, Bastuji-Garin S, Fangio P, et al. Sedation algorithm in critically ill patients without acute brain injury. Crit Care Med. 2005;33:120–7.
46. Anand KJS, Hansen DD, Hickey PR. Hormonal-metabolic stress responses in neonates undergoing cardiac surgery. Anesthesiology. 1990;73:661–70.
47. Anand KJS, Hickey PR. Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med. 1992;326:1–9.

48. Hansen-Flaschen JH, Brazinsky S, Basile C, Lanken PN. Use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure. JAMA. 1991;266:2870–5.
49. Kong KL, Willatts SM, Prys-Roberts C. Isoflurane compared with midazolam for sedation in the intensive care unit. BMJ. 1989;298:1277–80.
50. Tobias JD. Therapeutic applications and uses of inhalational anesthesia in the pediatric intensive care unit. Pediatr Crit Care Med. 2008;9:169–79.
51. Meiser A, Sirtl C, Bellgardt M, et al. Desflurane compared with propofol for postoperative sedation in the intensive care unit. Br J Anaesth. 2003;90: 273–80.
52. Bedi A, Murray JM, Dingley J, Stevenson MA, Fee JPH. Use of xenon as a sedative for patients receiving critical care. Crit Care Med. 2003;31:2470–7.
53. Satoh H, Gillette JR, Takemura T, et al. Investigation of the immunological basis of halothane-induced hepatotoxicity. Adv Exp Med Biol. 1986;197: 657–773.
54. Kenna JG, Neuberger J, Williams R. Evidence for expression in human liver of halothane-induced neoantigens recognized by antibodies in sera from patients with halothane hepatitis. Hepatology. 1988;8:1635–41.
55. Adams RW, Cucchiara RF, Gronert GA, Messick JM, Michenfelder JD. Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology. 1981;54:97–9.
56. Drummond JC, Todd MM, Scheller MS, Shapiro HM. A comparison of the direct cerebral vasodilating potencies of halothane and isoflurane in the New Zealand white rabbit. Anesthesiology. 1986;65: 462–7.
57. Reilly CS, Wood AJJ, Koshakji RP, Wood M. The effect of halothane on drug disposition: contribution of changes in intrinsic drug metabolizing capacity and hepatic blood flow. Anesthesiology. 1985;63:70–6.
58. Arnold JH, Truog RD, Rice SA. Prolonged administration of isoflurane to pediatric patients during mechanical ventilation. Anesth Analg. 1993;76: 520–6.
59. Sackey P, Martling CR, Granath F, Radell PJ. Prolonged isoflurane sedation of intensive care unit patients with the anesthetic conserving device. Crit Care Med. 2004;32:2241–6.
60. Sackey PV, Martling CR, Radell PJ. Three cases of PICU sedation with isoflurane delivered the "AnaConDa®". Pediatr Anesth. 2005;15:879–85.
61. Selander D, Curelaru I, Stefansson T. Local discomfort and thrombophlebitis following intravenous injection of diazepam. A comparison between a glycerol-water solution and a lipid emulsion. Acta Anaesthesiol Scand. 1981;25:516–8.
62. Forrest P, Galletly DC. A double-blind comparative study of three formulations of diazepam in volunteers. Anesth Intensive Care. 1988;16:158–63.
63. Reves JG, Fragan RJ, Vinik R, et al. Midazolam: pharmacology and uses. Anesthesiology. 1985;62:310–7.
64. Lloyd-Thomas AR, Booker PD. Infusion of midazolam in paediatric patients after cardiac surgery. Br J Anaesth. 1986;58:1109–15.
65. Silvasi DL, Rosen DA, Rosen KR. Continuous intravenous midazolam infusion for sedation in the pediatric intensive care unit. Anesth Analg. 1988;67:286–8.
66. Rosen DA, Rosen KR. Midazolam for sedation in the paediatric intensive care unit. Intensive Care Med. 1991;17:S15–9.
67. Jacqz-Algrain E, Daoud P, Burtin P, Desplanques L, Beaufils F. Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies. Lancet. 1994;344:646–50.
68. Beebe DS, Belani KG, Chang P, et al. Effectiveness of preoperative sedation with rectal midazolam, ketamine, or their combination in young children. Anesth Analg. 1992;75:880–4.
69. McMillian CO, Spahr-Schopfer IA, Sikich N, et al. Premedication of children with oral midazolam. Can J Anaesth. 1992;39:545–50.
70. Karl HW, Rosenberger JL, Larach MG, Ruffle JM. Transmucosal administration of midazolam for premedication of pediatric patients: comparison of the nasal and sublingual routes. Anesthesiology. 1993;78: 885–91.
71. Theroux MC, West DW, Cordry DH, et al. Efficacy of midazolam in facilitating suturing of lacerations in preschool children in the emergency department. Pediatrics. 1993;91:624–7.
72. Tobias JD. Subcutaneous administration of fentanyl and midazolam to prevent withdrawal following prolonged sedation in children. Crit Care Med. 1999;27:2262–5.
73. Cote CJ, Cohen IT, Suresh S, et al. A comparison of three doses of a commercially prepared oral midazolam syrup in children. Anesth Analg. 2002;94: 37–43.
74. Bauer TM, Ritz R, Haberthur C, et al. Prolonged sedation due to accumulation of conjugated metabolites of midazolam. Lancet. 1995;346:145–7.
75. Trouvin JH, Farinotti R, Haberer JP, et al. Pharmacokinetics of midazolam in anesthetized cirrhotic patients. Br J Anaesth. 1988;60:762–7.
76. Vinik HR, Reves JG, Greenblatt DJ, et al. The pharmacokinetics of midazolam in chronic renal failure patients. Anesthesiology. 1983;59:390–4.
77. de Wildt SN, de Hoog M, Vinks AA, et al. Population pharmacokinetics and metabolism of midazolam in pediatric intensive care unit patients. Crit Care Med. 2003;31:1952–8.
78. Payne K, Mattheyse FJ, Liebenberg D, et al. The pharmacokinetics of midazolam in paediatric patients. Eur J Clin Pharmacol. 1989;37:267–72.
79. Shapiro BA, Warren J, Egol AB, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Crit Care Med. 1995;23:1596–600.
80. Pohlman AS, Simpson KP, Hall JCB. Continuous intravenous infusions of lorazepam versus midazolam for sedation during mechanical ventilatory support:

a prospective, randomized study. Crit Care Med. 1994;22:1241–7.
81. Dundee JW, Johnston HM, Gray RC. Lorazepam as a sedative-amnestic in an intensive care unit. Curr Med Res Opin. 1976;4:290–5.
82. Lugo RA, Chester EA, Cash J, et al. A cost analysis of enterally administered lorazepam in the pediatric intensive care unit. Crit Care Med. 1999;27:417–21.
83. Tobias JD, Deshpande JK, Gregory DF. Outpatient therapy of iatrogenic drug dependency following prolonged sedation in the pediatric intensive care unit. Intensive Care Med. 1994;20:504–7.
84. Arbour R, Esparis B. Osmolar gap acidosis in a 60 year old man treated for hypoxemic respiratory failure. Chest. 2000;118:545–6.
85. Reynolds HN, Teiken P, Regan M, et al. Hyperlactatemia, increased osmolar gap, renal dysfunction during continuous lorazepam infusion. Crit Care Med. 2000;28:1631–4.
86. Arroliga AC, Shehab N, McCarthy K, Gonzales JP. Relationship of continuous infusion lorazepam to serum propylene glycol concentration in critically ill adults. Crit Care Med. 2004;32:1709–14.
87. Chicella M, Jansen P, Parthiban A, et al. Propylene glycol accumulation associated with continuous infusion of lorazepam in pediatric intensive care patients. Crit Care Med. 2002;30:2752–6.
88. Sfez M, Le Mapihan Y, Levron JC, Gaillard JL, Rosemblatt JM, Le Moing JP. Comparison of the pharmacokinetics of etomidate in children and adults. Ann Fran Anes Reanim. 1990;9:127–31.
89. Brussel T, Theissen JL, Vigfusson G, et al. Hemodynamic and cardiodynamic effects of propofol and etomidate: negative inotropic properties of propofol. Anesth Analg. 1989;69:35–40.
90. Kay B. A clinical assessment of the use of etomidate in children. Br J Anaesth. 1976;48:207–10.
91. Kay B. Total intravenous anesthesia with etomidate: evaluation of a practical technique for children. Acta Anaesth Belg. 1977;28:115–21.
92. Schechter WS, Kim C, Martinez M, Gleason BF, Lund DP, Burrows FA. Anaesthetic induction in a child with end-stage cardiomyopathy. Can J Anaesth. 1995;42:404–8.
93. Tobias JD. Etomidate: applications in pediatric anesthesia and critical care. J Intensive Care Med. 1997; 12:324–6.
94. Ching KY, Baum CR. Newer agents for rapid sequence intubation: etomidate and rocuronium. Pediatr Emerg Care. 2009;25:200–7.
95. Lehman KA, Mainka F. Ventilatory CO2-response after alfentanil and sedative premedication (etomidate, diazepam, and droperidol): a comparative study with human volunteers. Acta Anaesth Belg. 1986;37:3–13.
96. Choi SD, Spaulding BC, Gross JB, Apfelbaum JL. Comparison of the ventilatory effects of etomidate and methohexital. Anesthesiology. 1985;62:442–7.
97. Giese JL, Stockham RJ, Stanley TH, et al. Etomidate versus thiopental for induction of anesthesia. Anesth Analg. 1985;64:871–6.
98. Morgan M, Lumley J, Whitwam JG. Respiratory effects of etomidate. Br J Anaesth. 1977;49:233–6.
99. Renou AM, Vernhiet J, Macrez P, et al. Cerebral blood flow and metabolism during etomidate anaesthesia in man. Br J Anaesth. 1978;50:1047–51; Moss E, Powell D, Gibson RM, McDowall DG. Effect of etomidate on intracranial pressure and cerebral perfusion pressure. Br J Anaesth. 1979;51:347–52.
100. Modica PA, Tempellhoff R. Intracranial pressure during induction of anesthesia and tracheal intubation with etomidate-induced EEG burst suppression. Can J Anaesth. 1992;39:236–41.
101. Gancher S, Laxer KD, Krieger W. Activation of epileptogenic activity by etomidate. Anesthesiology. 1984;61:616–8.
102. Ebrahim ZY, DeBoer GE, Luders H, Hahn JF, Lesser RP. Effect of etomidate on the electroencephalogram of patients with epilepsy. Anesth Analg. 1986;65: 1004–6.
103. Ghoneim MM, Yamada T. Etomidate: a clinical and electroencephalographic comparison with thiopental. Anesth Analg. 1977;56:479–85.
104. Doenicke AW, Roizen MF, Kugler J, Kroll H, Foss J, Ostwald P. Reducing myoclonus after etomidate. Anesthesiology. 1999;90:113–9.
105. Patel A, Dallas SH. A trial of etomidate infusion anaesthesia for computerized axial tomography (letter). Anaesthesia. 1981;36:63.
106. Wagner RL, White PF, Kan PB, et al. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med. 1984;310:1415–8.
107. Annane D. ICU physicians should abandon the use of etomidate. Intensive Care Med. 2005;31:325–6.
108. Cotton BA, Guillamondegui OD, Fleming SB, et al. Increased risk of adrenal insufficiency following etomidate exposure in critically injured patients. Arch Surg. 2008;143:62–7.
109. Markowitz BP. The drug that would not die (though patients receiving it do) (editorial). Pediatr Crit Care Med. 2009;10:418–9.
110. Duthie DJR, Fraser R, Nimmo WS. Effect of induction of anaesthesia with etomidate on corticosteroid synthesis in man. Br J Anaesth. 1985;57:156–9.
111. Donmez A, Kaya H, Haberal A, Kutsal A, Arslan G. The effect of etomidate induction on plasma cortisol levels in children undergoing cardiac surgery. J Cardiothorac Vasc Anesth. 1998;12:182–5.
112. Absalom A, Pledger D, Kong A. Adrenocortical function in critically ill patients 24 hour after a single dose of etomidate. Anaesthesia. 1999;54:861–7.
113. Vinclair M, Broux C, Faure P, et al. Duration of adrenal inhibition following a single dose of etomidate in critically ill patients. Intensive Care Med. 2008;34: 714–9.
114. Ray DC, McKeown DW. Effect of induction agent on vasopressor and steroid use, and outcome in patients with septic shock. Crit Care. 2007;11:145–7.
115. Sprung CL, Annane D, Keh D, et al. CORTICUS study group: hydrocortisone therapy for patients with septic shock. JAMA. 2002;288:862–71.

116. Gelb AW, Lok P. Etomidate reversibly depresses human neutrophile chemiluminescence. Anesthesiology. 1987; 66:60–3.
117. Fazackerley EJ, Martin AJ, Tolhurst-Cleaver CL, Watkins J. Anaphylactoid reaction following the use of etomidate. Anaesthesia. 1988;43:953–4.
118. Olesen AS, Huttel MS, Hole P. Venous sequelae following the injection of etomidate or thiopentone IV. Br J Anaesth. 1984;56:171–3.
119. Nyman Y, Von Hofsten K, Palm C, et al. Etomidate-Lipuro® is associated with considerably less injection pain in children compared with propofol with added lidocaine. Br J Anaesth. 2006;97:536–9.
120. Bedicheck E, Kirschbaum B. A case of propylene glycol toxic reaction associated with etomidate infusion. Arch Intern Med. 1991;151:2297–8.
121. Levy ML, Aranda M, Selman V, Giannotta SL. Propylene glycol toxicity following continuous etomidate infusion for control of refractory cerebral edema. Neurosurgery. 1995;37:363–71.
122. Doenicke A, Roizen MF, Hoernecke R, Mayer M, Ostwald P, Foss J. Haemolysis after etomidate: comparison of propylene glycol and lipid formulations. Br J Anaesth. 1997;79:386–8.
123. Tobias JD. Airway management in the pediatric trauma patient. J Intensive Care Med. 1998;13:1–14.
124. Zhang J, Maland L, Hague B, et al. Buccal absorption of etomidate from a solid formulation in dogs. Anesth Analg. 1998;86:1116–22.
125. Linton DM, Thornington RE. Etomidate as a rectal induction agent. S Afr Med J. 1983;64:309–10.
126. Streisand JB, Haarsma RL, Gay MA, et al. Oral transmucosal etomidate in volunteers. Anesthesiology. 1998;88:89–95.
127. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic in man. Clin Pharmacol Ther. 1965;6:279–91.
128. Adriaenssens G, Vermeyen KM, Hoffmann VLH, Mertens E, Adriaensen HF. Postoperative analgesia with iv patient-controlled morphine: effect of adding ketamine. Br J Anaesth. 1999;83:393–6.
129. Jahangir SM, Islam F, Aziz L. Ketamine infusion for postoperative analgesia in asthmatics: comparison with intermittent meperidine. Anesth Analg. 1993; 76:45–9.
130. Himmelseher S, Durieux ME. Ketamine for perioperative pain management. Anesthesiology. 2005;102: 211–20.
131. Lahtinen P, Kokki H, Hakala T, et al. S(+) ketamine as an analgesic adjunct reduces opioid consumption after cardiac surgery. Anesth Analg. 2004;99:1295–301.
132. Chernow B, Laker R, Creuss D, et al. Plasma, urine, and cerebrospinal fluid catecholamine concentrations during and after ketamine sedation. Crit Care Med. 1982;10:600–3.
133. Wayman K, Shoemaker WC, Lippmann M. Cardiovascular effects of anesthetic induction with ketamine. Anesth Analg. 1980;59:355–8.
134. Spotoft H, Korshin JD, Sorensen MB, et al. The cardiovascular effects of ketamine used for induction of anesthesia in patients with valvular heart disease. Can Anaesth Soc J. 1979;26:463–7.
135. Gooding JM, Dimick AR, Travakoli M, et al. A physiologic analysis of cardiopulmonary responses to ketamine anesthesia in non-cardiac patients. Anesth Analg. 1977;56:813–6.
136. Morray JP, Lynn AM, Stamm SJ, et al. Hemodynamic effects of ketamine in children with congenital heart disease. Anesth Analg. 1984;63:895–9.
137. Hickey PR, Hansen DD, Cramolini GM, et al. Pulmonary and systemic hemodynamic responses to ketamine in infants with normal and elevated pulmonary vascular resistance. Anesthesiology. 1985;62: 287–93.
138. Wolfe RR, Loehr JP, Schaffer MS, Wiffins Jr JW. Hemodynamic effects of ketamine, hypoxia, and hyperoxia in children with surgically treated congenital heart disease residing ≥ 1,200 meters above sea level. Am J Cardiol. 1991;67:84–7.
139. Williams GD, Philip BM, Chu LF, et al. Ketamine does not increase pulmonary vascular resistance in children with pulmonary hypertension undergoing sevoflurane anesthesia and spontaneous ventilation. Anesth Analg. 2007;105:1578–84.
140. Singh A, Girotra S, Mehta Y, Radhakrishnan S, Shrivastava S. Total intravenous anesthesia with ketamine for pediatric interventional cardiac procedures. J Cardiothor Vasc Anesth. 2000;14:36–9.
141. Lebovic S, Reich DL, Steinberg G, Vela FP, Silvay G. Comparison of propofol versus ketamine for anesthesia in pediatric patients undergoing cardiac catheterization. Anesth Analg. 1992;74:490–4.
142. Mankikian B, Cantineau JP, Sartene R, et al. Ventilatory and chest wall mechanics during ketamine anesthesia in humans. Anesthesiology. 1986;65:492–9.
143. Von Ungern-Sternberg BS, Regli A, Frei FJ, et al. A deeper level of ketamine anesthesia does not affect functional residual capacity and ventilation distribution in healthy preschool children. Pediatr Anesth. 2007;17:1150–5.
144. Hirshman CA, Downes H, Farbood A, Bergman NA. Ketamine block of bronchospasm in experimental canine asthma. Br J Anaesth. 1979;51:713–8.
145. Bourke DL, Malit LA, Smith TC. Respiratory interactions of ketamine and morphine. Anesthesiology. 1987;66:153–6.
146. Lanning CF, Harmel MH. Ketamine anesthesia. Annu Rev Med. 1975;26:137–41.
147. Taylor PA, Towey RM. Depression of laryngeal reflexes during ketamine administration. Br Med J. 1971;2:688–9.
148. Berkenbosch JW, Graff GR, Stark JM. Safety and efficacy of ketamine sedation for infant flexible fiberoptic bronchoscopy. Chest. 2004;125:1132–7.
149. Shapiro HM, Wyte SR, Harris AB. Ketamine anesthesia in patients with intracranial pathology. Br J Anaesth. 1972;44:1200–4.
150. Gardner AE, Dannemiller FJ, Dean D. Intracranial cerebrospinal fluid pressure in man during ketamine anesthesia. Anesth Analg. 1972;51:741–5.

151. Reicher D, Bhalla P, Rubinstein EH. Cholinergic cerebral vasodilator effects of ketamine in rabbits. Stroke. 1987;18:445–9.
152. Oren RE, Rasool NA, Rubinstein EH. Effect of ketamine on cerebral cortical blood flow and metabolism in rabbits. Stroke. 1987;18:441–4.
153. Pfenninger E, Dick W, Ahnefeld FW. The influence of ketamine on both the normal and raised intracranial pressure of artificially ventilated animals. Eur J Anaesth. 1985;2:297–307.
154. Pfenninger E, Grunert A, Bowdler I, Kilian J. The effect of ketamine on intracranial pressure during haemorrhagic shock under the conditions of both spontaneous breathing and controlled ventilation. Acta Neurochir. 1985;78:113–8.
155. Albanese J, Arnaud S, Rey M, et al. Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. Anesthesiology. 1997;87:1328–34.
156. Bourgoin A, Albanese J, Wereszczynski N, Charbit M, Vialet R, Martin C. Safety of sedation with ketamine in severe head injury patients: comparison with sufentanil. Crit Care Med. 2003;31:711–7.
157. Mayberg TS, Lam AM, Matta BF, Domino KB, Winn R. Ketamine does not increase cerebral blood flow velocity of intracranial pressure during isoflurane/nitrous oxide anesthesia in patients undergoing craniotomy. Anesth Analg. 1995;81:84–9.
158. Shapira Y, Lam AM, Artru AA, Eng C, Soltow L. Ketamine alters calcium and magnesium in brain tissue following experimental head trauma in rats. J Cereb Blood Flow Metab. 1993;13:962–9.
159. Rosen I, Hagerdal M. Electroencephalographic study of children during ketamine anesthesia. Acta Anaesthesiol Scand. 1976;20:32–9.
160. Manohar S, Maxwell D, Winters WD. Development of EEG seizure activity during and after chronic ketamine administration in the rat. Neuropharmacology. 1972;11:819–26.
161. Bourn WM, Yang DJ, Davisson JN. Effect of ketamine enantiomers on sound-induced convulsions in epilepsy prone rats. Pharm Res Commun. 1983;15:815–24.
162. Veliskova J, Velisek L, Mares P, Rokyta R. Ketamine suppresses both bicuculline and picrotoxin induced generalized tonic clonic seizures during ontogenesis. Pharm Biochem Behav. 1990;37:667–74.
163. Sheth RD, Gidal BE. Refractory status epilepticus: response to ketamine. Neurology. 1998;51:1765–6.
164. Haeseler G, Zuzan O, Kohn G, et al. Anaesthesia with midazolam and S-(+) ketamine in spontaneously breathing paediatric patients during magnetic resonance imaging. Paediatr Anaesth. 2000;10:513–9.
165. Pees C, Haas NA, Ewert P, et al. Comparison of analgesia and sedative effect of racemic ketamine and S(+) ketamine during cardiac catheterization in newborns and children. Pediatr Cardiol. 2003;24:424–9.
166. Marhofer P, Freitag H, Hochtl A, et al. S(+) ketamine for rectal premedication in children. Anesth Analg. 2001;92:62–5.
167. Koinig H, Marhoger P. S(+) ketamine in paediatric anaesthesia. Paediatr Anaesth. 2003;13:185–7.
168. Tobias JD, Martin LD, Wetzel RC. Ketamine by continuous infusion for sedation in the pediatric intensive care unit. Crit Care Med. 1990;18:819–21.
169. Hartvig P, Larsson E, Joachimsson PO. Postoperative analgesia and sedation following pediatric cardiac surgery using a constant infusion of ketamine. J Cardiothorac Vasc Anesth. 1993;7:148–53.
170. Edrich T, Friedrich AD, Eltzschig HK, Felbinger TW. Ketamine for long-term sedation and analgesia of a burn patient. Anesth Analg. 2004;99:893–5.
171. Weksler N, Ovadia L, Muati G, et al. Nasal ketamine for paediatric premedication. Can J Anaesth. 1993;40:119–21.
172. Weber F, Wulf H, el Saeidi G. Premedication with nasal s-ketamine and midazolam provides good conditions for induction of anaesthesia in preschool children. Can J Anaesth. 2003;50:470–5.
173. Sebel PS, Lowdon JD. Propofol: a new intravenous anesthetic. Anesthesiology. 1989;71:260–77.
174. Harris CE, Grounds RM, Murray AM, et al. Propofol for long-term sedation in the intensive care unit. A comparison with papaveretum and midazolam. Anaesthesia. 1990;45:366–72.
175. Beller JP, Pottecher T, Lugnier A, et al. Prolonged sedation with propofol in ICU patients: recovery and blood concentration changes during periodic interruption in infusion. Br J Anaesth. 1988;61:583–8.
176. Ronan KP, Gallagher TJ, George B, Hamby B. Comparison of propofol and midazolam for sedation in intensive care unit patients. Crit Care Med. 1995;23:286–93.
177. Hemelrijck JV, Fitch W, Mattheussen M, Van Aken H, Plets C, Lauwers T. Effect of propofol on cerebral circulation and autoregulation in the baboon. Anesth Analg. 1990;71:49–54.
178. Nimkoff L, Quinn C, Silver P, Sagy M. The effects of intravenous anesthetic agents on intracranial pressure and cerebral perfusion pressure in two feline models of brain edema. J Crit Care. 1997;12:132–6.
179. Watts ADJ, Eliasziw M, Gelb AW. Propofol and hyperventilation for the treatment of increased intracranial pressure in rabbits. Anesth Analg. 1998;87:564–8.
180. Herregods L, Verbeke J, Rolly G, Colardyn F. Effect of propofol on elevated intracranial pressure. Preliminary results. Anaesthesia. 1988;43(Suppl):107–9.
181. Pinaud M, Lelausque J, Chetanneau A, Fauchoux N, Menegalli D, Souron R. Effects of propofol on cerebral hemodynamics and metabolism in patients with brain trauma. Anesthesiology. 1990;73:404–9.
182. Mangez JF, Menguy E, Roux P. Sedation par propofol a debit constant chez le traumatise cranien. Resultas preliminaires. Ann Fr Anesth Reanim. 1987;6:336–7.
183. Ravussin P, Guinard JP, Ralley F, Thorin D. Effect of propofol on cerebrospinal fluid pressure and cerebral perfusion pressure in patients undergoing craniotomy. Anaesthesia. 1988;43(Suppl):107–9.

184. Farling PA, Johnston JR, Coppel DL. Propofol infusion for sedation of patients with head injury in intensive care. Anaesthesia. 1989;44:222–6.
185. Yamaguchi S, Midorikawa Y, Okuda Y, et al. Propofol prevents delayed neuronal death following transient forebrain ischemia in gerbils. Can J Anaesth. 1999;46:593–8.
186. Young Y, Menon DK, Tisavipat N, et al. Propofol neuroprotection in a rat model of ischaemia reperfusion injury. Eur J Anesthesiol. 1997;14:320–6.
187. Fox J, Gelb AW, Enns J, et al. The responsiveness of cerebral blood flow to changes in arterial carbon dioxide is maintained during propofol-nitrous oxide anesthesia in humans. Anesthesiology. 1992;77: 453–6.
188. Eames WO, Rooke GA, Sai-Chuen R, Bishop MJ. Comparison of the effects of etomidate, propofol, and thiopental on respiratory resistance after tracheal intubation. Anesthesiology. 1996;84:1307–11.
189. Pizov R, Brown RH, Weiss YS, et al. Wheezing during induction of general anesthesia in patients with and without asthma. A randomized, blinded trial. Anesthesiology. 1995;82:1111–6.
190. Chih-Chung L, Ming-Hwang S, Tan PPC, et al. Mechanisms underlying the inhibitory effect of propofol on the contraction of canine airway smooth muscle. Anesthesiology. 1999;91:750–9.
191. Pedersen CM, Thirstrup S, Nielsen-Kudsk JE. Smooth muscle relaxant effects of propofol and ketamine in isolated guinea-pig tracheas. Eur J Pharm. 1993;238:75–80.
192. Brown RH, Greenberg RS, Wagner EM. Efficacy of propofol to prevent bronchoconstriction. Anesthesiology. 2001;94:851–5.
193. Rieschke P, LeFleur BJ, Janicki PK. Effects of EDTA and sulfite-containing formulations of propofol on respiratory system resistance after tracheal intubation in smokers. Anesthesiology. 2003;98:323–8.
194. Tritapepe L, Voci P, Marino P, et al. Calcium chloride minimizes the hemodynamic effects of propofol in patients undergoing coronary artery bypass grafting. J Cardiothorac Vasc Anesth. 1999;13:150–3.
195. Sochala C, Van Deenen D, De Ville A, Govaerts MJM. Heart block following propofol in a child. Paediatr Anaes. 1999;9:349–51.
196. Egan TD, Brock-Utne JG. Asystole and anesthesia induction with a fentanyl, propofol, and succinylcholine sequence. Anesth Analg. 1991;73:818–20.
197. Kannan S, Sherwood N. Termination of supraventricular tachycardia by propofol. Br J Anaesth. 2002;88:874–5.
198. Trotter C, Serpell MG. Neurological sequelae in children after prolonged propofol infusions. Anaesthesia. 1992;47:340–2.
199. Saunders PRI, Harris MNE. Opisthotonic posturing and other unusual neurological sequelae after outpatient anesthesia. Anaesthesia. 1992;47:552–7.
200. Finley GA, MacManus B, Sampson SE, Fernandez CV, Retallick I. Delayed seizures following sedation with propofol. Can J Anaesth. 1993;40:863–5.
201. Hewitt PB, Chu DLK, Polkey CE, Binnie CD. Effect of propofol on the electrocorticogram in epileptic patients undergoing cortical resection. Br J Anaesth. 1999;82:199–202.
202. McBurney JW, Teiken PJ, Moon MR. Propofol for treating status epilepticus. J Epilepsy. 1994;7:21–2.
203. Lowenstein DH, Alldredge BK. Status epilepticus. New Engl J Med. 1998;338:970–6.
204. Parke TJ, Stevens JE, Rice ASC, et al. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. Br Med J. 1992;305:613–6.
205. Strickland RA, Murray MJ. Fatal metabolic acidosis in a pediatric patient receiving an infusion of propofol in the intensive care unit: is there a relationship? Crit Care Med. 1995;23:405–9.
206. Hanna JP, Ramundo ML. Rhabdomyolysis and hypoxia associated with prolonged propofol infusion. Neurology. 1998;50:301–3.
207. Bray RJ. Propofol infusion syndrome in children. Paediatr Anaesth. 1998;8:491–9.
208. Spitzfadden AC, Jimenez DF, Tobias JD. Propofol for sedation and control of intracranial pressure in children. Pediatr Neurosurg. 1999;31:194–200.
209. Cremer OL, Bouman EAC, Kruijswijk JE, et al. Long-term propofol infusion and cardiac failure in adult head-injured patients. Lancet. 2000;357:117–8.
210. Perrier ND, Baerga-Varela Y, Murray M. Death related to propofol use in an adult. Crit Care Med. 2000;28:3071–4.
211. Schenkman KA, Yan S. Propofol impairment of mitochondrial respiration in isolated perfused guinea pig hearts determined by reflectance spectroscopy. Crit Care Med. 2000;28:172–7.
212. Wolf A, Weir P, Segar P, et al. Impaired fatty acid oxidation in propofol infusion syndrome. Lancet. 2001;357:606–7.
213. Withington DE, Decell MK, Al Ayed T. A case of propofol toxicity: further evidence for a causal mechanism. Pediatr Anesth. 2004;14:505–8.
214. Rigby-Jones AE, Nolan JA, Priston MJ, et al. Pharmacokinetics of propofol infusions in critically ill neonates, infants, and children in an intensive care unit. Anesthesiology. 2002;97:1393–400.
215. Reed MD, Yamashita TS, Marz CM, et al. A pharmacokinetically based propofol dosing strategy for sedation of the critically ill, mechanically ventilated pediatric patient. Crit Care Med. 1996;24:1473–81.
216. Norreslet J, Wahlgreen C. Propofol infusion for sedation of children. Crit Care Med. 1990;18:890–2.
217. Playfor SD, Venkatesh K. Current patterns of propofol use in the United Kingdom and North America. Pediatr Anesth. 2004;14:501–4.
218. Cornfield DN, Tegtmeyer K, Nelson MD, et al. Continuous propofol infusion in 142 critically ill children. Pediatrics. 2002;110:1177–81.
219. Committee on Safety of Medicines, Medicines Control Agency. Propofol (diprivan) infusion: sedation in children aged 16 years or younger. Curr Probl Pharmacovigil. 2001;27:10.

220. Cravens GT, Pcker DL, Johnson ME. Incidence of propofol infusion syndrome during noninvasive radiofrequency ablation for atrial flutter or fibrillation. Anesthesiology. 2007;106:1134–8.
221. Hertzog JH, Campbell JK, Dalton HJ, Hauser GJ. Propofol anesthesia for invasive procedures in ambulatory and hospitalized children: experience in the pediatric intensive care unit. Pediatrics. 1999;103:e30.
222. Reeves ST, Havidick JE, Tobin P. Conscious sedation of children with propofol is anything but conscious. Pediatrics. 2004;114:e74.
223. Laxenaire MC, Mata-Bermejo E, Moneret-Vautrin DA, Gueant JL. Life-threatening anaphylactoid reactions to propofol. Anesthesiology. 1992;77:275–80.
224. Gottardis M, Khunl-Brady KS, Koller W, et al. Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations. Br J Anaesth. 1989;62:393–6.
225. Valente JF, Anderson GL, Branson RD, et al. Disadvantages of prolonged propofol sedation in the critical care unit. Crit Care Med. 1994;22:710–2.
226. Camps AS, Sanchez-Izquierdo Riera JA, Vazquez DT, et al. Midazolam and 2% propofol in long-term sedation of traumatized, critically ill patients: efficacy and safety comparison. Crit Care Med. 2000;28:3612–9.
227. Barrientos-Vega R, Sanchez-Soria M, Morales-Garcia C, et al. Pharmacoeconomic assessment of propofol 2% used for prolonged sedation. Crit Care Med. 2001;29:317–22.
228. Song D, Hamza MA, White PF, et al. Comparison of a lower-lipid propofol emulsion with the standard emulsion for sedation during monitored anesthesia care. Anesthesiology. 2004;100:1072–5.
229. Campos AS, Sanchez-Izquierdo R, Vazquez DT, et al. Midazolam and 2% propofol in long-term sedation of traumatized, critically ill patients: efficacy and safety comparison. Crit Care Med. 2000;28:3612–9.
230. Griffin J, Ray T, Gray B, et al. Pain on injection of propofol: a thiopental/propofol mixture versus a lidocaine/propofol mixture. Am J Pain Manage. 2002;12:45–9.
231. Tobias JD. Prevention of pain associated with the administration of propofol in children: lidocaine versus ketamine. Am J Anesthesiol. 1996;23:231–2.
232. Picard P, Tramer MR. Prevention of pain on injection with propofol: a quantitative systematic review. Anesth Analg. 2000;90:963–9.
233. Mangar D, Holak EJ. Tourniquet at 50 mmHg followed by intravenous lidocaine diminishes hand pain associated with propofol injection. Anesth Analg. 1992;74:250–2.
234. Haugen RD, Vaghadia H, Waters T, Merick PM. Thiopentone pretreatment for propofol injection pain in ambulatory patients. Can J Anaesth. 1993;42:1108–12.
235. Sosis MB, Braverman B. Growth of *Staphylococcus aureus* in four intravenous anesthetics. Anesth Analg. 1993;77:766–8.
236. Centers for Disease Control (CDC). Postsurgical infections associated with extrinsically contaminated intravenous anesthetic agent – California, Illinois, Maine, and Michigan. MMWR Morb Mortal Wkly Rep. 1990;39:426–7, 433.
237. Trissel LA, Gilbert DL, Martinez JF. Drug compatibility differences with propofol injectable emulsion products with selected drugs during simulated Y-site administration. Am J Health Syst Pharm. 1997;54:1287–92.
238. Lewis TC, Janicki PK, Higgins MS, et al. Anesthetic potency of propofol with disodium edetate versus sulfite-containing propofol in patients undergoing magnetic resonance imaging: a retrospective analysis. Am J Anesthesiol. 2000;27:30–2.
239. Fassoulaki A, Paraskeva A, Papilas K, Patris K. Hypnotic and cardiovascular effects of proprietary and generic propofol formulations do not differ. Can J Anaesth. 2001;48:459–61.
240. Astrup J, Sorensen PM, Sorensen HR. Inhibition of cerebral oxygen and glucose consumption in the dog by hypothermia, pentobarbital and lidocaine. Anesthesiology. 1981;55:263–8.
241. Cormio M, Gopinath SP, Valadka A, et al. Cerebral hemodynamic effects of pentobarbital coma in head-injured patients. J Neurotrauma. 1999;16:927–36.
242. Krishnamurthy KB, Drislane FW. Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus. Epilepsia. 1999;40:759–62.
243. Holmes GL, Riviello Jr JJ. Midazolam and pentobarbital for refractory status epilepticus. Pediatr Neurol. 1999;20:259–64.
244. Ishimaru H, Takahashi A, Ikarashi Y, et al. Effects of MK-801 and pentobarbital on cholinergic terminal damage and delayed neuronal death in the ischemic gerbil hippocampus. Brain Res Bull. 1997;43:81–5.
245. Morimoto Y, Morimoto Y, Nishihira J, et al. Pentobarbital inhibits apoptosis in neuronal cells. Crit Care Med. 2000;28:1899–904.
246. Tobias JD, Deshpande JK, Pietsch JB, Wheeler TJ, Gregory DG. Pentobarbital sedation in the pediatric intensive care unit patient. South Med J. 1995;88:290–4.
247. Tobias JD. Pentobarbital for sedation during mechanical ventilation in the pediatric ICU patient. J Intensive Care Med. 2000;15:115–20.
248. Yanay O, Brogan TV, Martin LD. Continuous pentobarbital infusion in children is associated with high rates of complications. J Crit Care. 2004;19:174–8.
249. Audenaert SM, Montgomery CL, Thompson DE, et al. A prospective study of rectal methohexital: efficacy and side effects in 648 cases. Anesth Analg. 1995;81:957–61.
250. Nguyen MT, Greenburg SB, Fitzhugh KR, et al. Pediatric imaging: sedation with an injection formulation modified for rectal administration. Radiology. 2001;221:760–2.

251. Alp H, Orbak Z, Guler I, et al. Efficacy and safety of rectal thiopental, intramuscular cocktail and rectal midazolam for sedation in children undergoing neuroimaging. Pediatr Int. 2002;44:628–34.
252. Strain JD, Campbell JB, Harvey LA, et al. IV nembutal: safe sedation for children undergoing CT. Am J Roentgenol. 1988;151:975–9.
253. Malviya S, Voepel-Lewis T, Tait AR, et al. Pentobarbital versus chloral hydrate for sedation of children undergoing MRI: efficacy and recovery characteristics. Pediatr Anesth. 2004;14:589–95.
254. Dershwitz M, Rosow CE, DiBiase PM, Zaslavsky A. Comparison of the sedative effects of butorphanol and midazolam. Anesthesiology. 1991;74: 717–24.
255. Burkle H, Dunbar S, Van Aken H. Remifentanil: a novel, short acting, mu opioid. Anesth Analg. 1996; 83:646–51.
256. Kinder Ross A, Davis PJ, deL Dear G, et al. Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. Anesth Analg. 2001; 93:1393–401.
257. Cavaliere F, Antonelli M, Arcangeli A, et al. A low-dose remifentanil infusion is well tolerated for sedation in mechanically ventilated, critically ill patients. Can J Anesth. 2002;49:1088–94.
258. Dahaba AA, Rabner T, Rehak PH, List WF, Metzler H. Remifentanil versus morphine analgesia and sedation for mechanically ventilated critically ill patients. Anesthesiology. 2004;101:640–6.
259. Tobias JD. Remifentanil: applications in the pediatric ICU population. Am J Pain Manage. 1998;8:114–7.
260. Vinik HR, Kissin I. Rapid development of tolerance to analgesia during remifentanil infusion in humans. Anesth Analg. 1998;86:1307–11.
261. Guignard B, Bossard AE, Coste C, et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology. 2000;93:409–17.
262. Keidan I, Berkenstadt H, Sidi A, et al. Propofol-remifentanil versus propofol alone for bone marrow aspiration in paedaitric haemato-oncological patients. Paediatr Anaesth. 2001;11:297–301.
263. Reyle-Hahn M, Niggemann B, Max M, et al. Remifentanil and propofol for sedation in children and young adolescents undergoing diagnostic flexible bronchoscopy. Paediatr Anaesth. 2000; 10:59–63.
264. Litman RS. Conscious sedation with remifentanil and midazolam during brief painful procedures in children. Arch Paediatr Adolesc Med. 1999;153:1085–8.
265. Sperry RJ, Bailey PL, Reuchman MV, et al. Fentanyl and sufentanil increase intracranial pressure in head trauma patients. Anesthesiology. 1992;77:416–20.
266. Milde LN, Milde JH, Gallagher WJ. Effects of sufentanil on cerebral circulation and metabolism in dogs. Anesth Analg. 1990;70:138–46.
267. Pokela ML, Ryhanen PT, Koivisto ME, et al. Alfentanil-induced rigidity in newborn infants. Anesth Analg. 1992;75:252–7.
268. Glick C, Evans OB, Parks BR. Muscle rigidity due to fentanyl infusion in the pediatric patient. South Med J. 1996;89:1119–20.
269. MacGregor R, Evans D, Sugden D, et al. Outcome at 5–6 years of prematurely born children who received morphine as neonates. Arch Dis Child Fetal Neonatal. 1998;79:F40–3.
270. Lynn AM, Opheim KE, Tyler DC. Morphine infusion after pediatric cardiac surgery. Crit Care Med. 1984;12:863–6.
271. Quinn MW, Wild J, Dean HG, et al. Randomised double-blind controlled trial of effect of morphine on catecholamine concentrations in ventilated preterm babies. Lancet. 1993;342:324–7.
272. Franck LS, Vilardi J, Durand D, et al. Opioid withdrawal in neonates after continuous infusions of morphine or fentanyl during extracorporeal membrane oxygenation. Am J Crit Care. 1998;7:364–9.
273. Bruera E, Brenneis C, Michaud M, et al. Use of the subcutaneous route for the administration of narcotics in patients with cancer pain. Cancer. 1988; 62:407–11.
274. Bruera E, Gibney N, Stollery D, Marcushamer S. Use of the subcutaneous route of administration of morphine in the intensive care unit. J Pain Symptom Manage. 1991;6:263–5.
275. Tobias JD, O'Connor TA. Subcutaneous administration of fentanyl for sedation during mechanical ventilation in an infant. Am J Pain Manage. 1996; 6:115–7.
276. Dietrich CC, Tobias JD. Subcutaneous fentanyl infusions in the pediatric population. Am J Pain Manage. 2003;13:146–50.
277. Suzuki S, Carlos MP, Chuang LF, et al. Methadone induces CCR5 and promotes AIDS virus infection. FEBS Lett. 2002;519:173–7.
278. Carr DJ, Rogers TJ, Weber RJ. The relevance of opioids and opioid receptors on immunocompetence and immune homeostasis. Proc Soc Exp Biol Med. 1996;213:248–57.
279. Tubaro E, Borelli G, Croce C, Cavallo G, Santiangeli C. Effect of morphine on resistance to infection. J Infect Dis. 1983;148:656–66.
280. Froemming JS, Lam YWF, Jann MW, Davis CM. Pharmacokinetics of haloperidol. Clin Pharmacokinet. 1989;17:396–423.
281. Harvey MA. Managing agitation in critically ill adults. Am J Crit Care. 1996;5:7–16.
282. Riker RR, Fraser GL, Cox PM. Continuous infusions of haloperidol controls agitation in critically ill patients. Crit Care Med. 1994;22:433–40.
283. Milbrandt EB, Alexander K, Kong L, et al. Haloperidol is associated with lower hospital mortality in mechanically ventilated patients. Crit Care Med. 2005;33:226–9.

284. Harrison AM, Lugo RA, Lee WE, et al. The use of haloperidol in agitated critically ill children. Clin Pediatr. 2002;41:51–4.
285. Schuderi PE. Droperidol: many questions, few answers. Anesthesiology. 2003;98:289–90.
286. US Food and Drug Administration MedWatch. http://www.fda/gov/medwatch/SAFETY/2001/inapsine.htm. Accessed 8 Jun 2011.
287. Correa-Sales C, Reid K, Maze M. Pertussis toxin mediated ribosylation of G proteins blocks the hypnotic response to an alpha2 agonist in the locus cereleus of the rat. Pharmacol Biochem Behav. 1992;43:723–7.
288. Correa-Sales C, Nacif-Coelho C, Reid K, Maze M. Inhibition of adenylate cyclase in the locus cereleus mediates the hypnotic response to an alpha2 agonist in the rat. J Pharmacol Exp Ther. 1992;263:1046–50.
289. Nacif-Coelho C, Correa-Sales C, Chang LL, Maze M. Perturbation of ion channel conductance alters the hypnotic response to the alpha2 adrenergic agonist dexmedetomidine in the locus cereleus of the rat. Anesthesiology. 1994;81:1527–34.
290. Sculptoreanu A, Scheuer T, Catterall WA. Voltage-dependent potentiation of L-type Ca2+ channels due to phosphorylation by cAMP-dependent protein kinase. Nature. 1993;364:240–3.
291. Correa-Sales C, Rabin BC, Maze M. A hypnotic response to dexmedetomidine, an alpha2 agonist is mediated in the locus cereleus in rats. Anesthesiology. 1992;76:948–52.
292. Doze VA, Chen BX, Maze M. Dexmedetomidine produces a hypnotic-anesthetic action in rats via activation of central alpha-2 adrenoceptors. Anesthesiology. 1989;71:75–9.
293. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology. 2003;98:428–36.
294. Maze MM, Tranquilli W. Alpha-2 agonists: defining the role in clinical anesthesia. Anesthesiology. 1991;74:581–91.
295. Mikawa K, Maekawa N, Nishina K, et al. Efficacy of oral clonidine premedication in children. Anesthesiology. 1993;79:926–31.
296. De Kock MF, Pichon G, Scholtes JL. Intraoperative clonidine enhances postoperative morphine patient-controlled analgesia. Can J Anaesth. 1992;39:537–44.
297. Bohrer H, Bach A, Layer M, Werning P. Clonidine as a sedative adjunct in intensive care. Intensive Care Med. 1990;16:265–6.
298. Ambrose C, Sale S, Howells R, et al. Intravenous clonidine infusion in critically ill children: dose-dependent sedative effects and cardiovascular stability. Br J Anaesth. 2000;84:794–6.
299. Arenas-Lopez S, Riphagen S, Tibby SM, et al. Use of oral clonidine for sedation in ventilated pediatric intensive care patients. Intensive Care Med. 2004;30:1625–9.
300. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med. 2007;8:115–31.
301. Hall JE, Uhrich TD, Barney JA, et al. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg. 2000;90:699–705.
302. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of post-operative patients requiring intensive care. Br J Anaesth. 2002;88:669–75.
303. Tobias JD, Berkenbosch JW. Sedation during mechanical ventilation in infants and children: dexmedetomidine versus midazolam. South Med J. 2005;97:451–5.
304. Berkenbosch JW, Tobias JD. Development of bradycardia during sedation with dexmedetomidine in an infant concurrently receiving digoxin. Pediatr Crit Care Med. 2003;4:203–5.
305. Koroglu A, Demirbilek S, Teksan H, et al. Sedative, hemodynamic and respiratory effects of dexmedetomidine in children undergoing magnetic resonance imaging examination: preliminary results. Br J Anaesth. 2005;94:821–4.
306. Berkenbosch JW, Wankum P, Tobias JD. Prospective evaluation of dexmedetomidine for noninvasive procedural sedation in children. Pediatr Crit Care Med. 2005;6:435–9.
307. Koroglu A, Teksan H, Sagir O, et al. A comparison of the sedative, hemodynamic and respiratory effects of dexmedetomidine and propofol in children undergoing magnetic resonance imaging. Anesth Analg. 2006;103:63–7.
308. Mason KP, Zgleszewski SE, Dearden JL, et al. Dexmedetomidine for pediatric sedation for computed tomography imaging studies. Anesth Analg. 2006;103:57–62.
309. Scher CS, Gitlin MC. Dexmedetomidine and low-dose ketamine provide adequate sedation for awake fibreoptic intubation. Can J Anesth. 2003;50:607–10.
310. Tosun Z, Akin A, Guler G, et al. Dexmedetomidine-ketamine and propofol-ketamine combinations for anesthesia in spontaneously breathing pediatric patients undergoing cardiac catheterization. J Cardiothorac Vasc Anesth. 2006;20:515–9.
311. Mester R, Easley RB, Brady KM, et al. Monitored anesthesia care with a combination of dexmedetomidine and ketamine during cardiac catheterization. Am J Ther. 2008;15:24–30.
312. Levanen J, Makela ML, Scheinin H. Dexmedetomidine premedication attenuates ketamine-induced cardiostimulatory effects and postanesthetic delirium. Anesthesiology. 1995;82:1117–25.
313. Riihioja P, Jaatinen P, Oksanen H, et al. Dexmedetomidine, diazepam, and propranolol in the treatment of alcohol withdrawal symptoms in the rat. Alcohol Clin Exp Res. 1997;21:804–8.
314. Riihioja P, Jaatinen P, Haapalinna A, et al. Effects of dexmedetomidine on rat loceus coeruleus and etha-

nol withdrawal symptoms during intermittent ethanol exposure. Alcohol Clin Exp Res. 1999;23:432–8.
315. Riihioja P, Jaatinen P, Oksanen H, et al. Dexmedetomidine alleviates ethanol withdrawal symptoms in the rat. Alcohol. 1997;14:537–44.
316. Riihioja P, Jaatinen P, Haapalinna A, et al. Prevention of ethanol-induced sympathetic overactivity and degeneration by dexmedetomidine. Alcohol. 1995;12:439–46.
317. Maccioli GA. Dexmedetomidine to facilitate drug withdrawal. Anesthesiology. 2003;98:575–7.
318. Multz AS. Prolonged dexmedetomidine infusion as an adjunct in treating sedation-induced withdrawal. Anesth Analg. 2003;96:1054–5.
319. Finkel JC, Elrefai A. The use of dexmedetomidine to facilitate opioid and benzodiazepine detoxification in an infant. Anesth Analg. 2004;98:1658–9.
320. Baddigam K, Russo P, Russo J, et al. Dexmedetomidine in the treatment of withdrawal syndromes in cardiothoracic surgery patients. J Intensive Care Med. 2005;20:118–23.
321. Finkel JC, Johnson YJ, Quezado YMN. The use of dexmedetomidine to facilitate acute discontinuation of opioids alter cardiac transplantation in children. Crit Care Med. 2005;33:2110–2.
322. Tobias JD. Dexmedetomidine to treat opioid withdrawal in infants and children following prolonged sedation in the pediatric ICU. J Opioid Manage. 2006;2:201–6.
323. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. Anesthesiology. 1992;77:1125–33.
324. Talke P, Chen R, Thomas B, et al. The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. Anesth Analg. 2000;90:834–83.
325. Peden CJ, Cloote AH, Stratford N, Prys-Roberts C. The effect of intravenous dexmedetomidine premedication on the dose requirement of propofol to induce loss of consciousness in patients receiving alfentanil. Anaesthesia. 2001;56:408–13.
326. Hammer GB, Drover DR, Cao H, et al. The effects of dexmedetomidine on cardiac electrophysiology in children. Anesth Analg. 2008;106:79–83.
327. Chrysostomou C, Beerman L, Shiderly D, et al. Dexmedetomidine: a novel drug for the treatment of atrial and junctional tachyarrhythmias during the perioperative period for congenital cardiac surgery: a preliminary study. Anesth Analg. 2008;107:1514–22.
328. Prielipp RC, Wall MH, Tobin JR, et al. Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. Anesth Analg. 2002;95:1052–9.
329. Zornow MH, Scheller MS, Sheehan PB, Strenat MA, Matsumoto M. Intracranial pressure effects of dexmedetomidine in rabbits. Anesth Analg. 1992;75:232–7.
330. Talke P, Tong C, Lee HW, et al. Effect of dexmedetomidine on lumbar cerebrospinal fluid pressure in humans. Anesth Analg. 1997;85:358–64.
331. Kuhmonen J, Haapalinna A, Sivenius J. Effects of dexmedetomidine after transient and permanent occlusion of the middle cerebral artery in the rat. J Neural Transm. 2001;108:261–71.
332. Hoffman WE, Kochs E, Werner C, Thomas C, Albrecht RF. Dexmedetomidine improves neurologic outcome from incomplete ischemia in the rat. Reversal by the alpha-2 adrenergic antagonist atipamezole. Anesthesiology. 1991;75:328–32.
333. Kuhmonen J, Pokorny J, Miettinen R, et al. Neuroprotective effects of dexmedetomidine in the gerbil hippocampus after transient global ischemia. Anesthesiology. 1997;87:371–7.
334. Miyazaki Y, Adachi T, Kurata J, Utsumi J, et al. Dexmedetomidine reduces seizure threshold during enflurane anaesthesia in cats. Br J Anaesth. 1999;82:935–7.
335. Whittington RA, Virag L, Vulliemoz Y, et al. Dexmedetomidine increases the cocaine seizure threshold in rats. Anesthesiology. 2002;97:693–700.
336. Tanaka K, Oda Y, Funao T, et al. Dexmedetomidine decreases the convulsive potency of bupivacaine and levobupivacaine in rats: Involvement of α2-adrenoceptor for controlling convulsions. Anesth Analg. 2005;100:687–96.
337. Mirski MA, Rossell LA, McPherson RW, Traystman RJ. Dexmedetomidine decreases seizure threshold in a rat model of experimental generalized epilepsy. Anesthesiology. 1994;81:1422–8.
338. Keeter S, Benator RM, Weinberg SM, Hartenberg MA. Sedation in pediatric CT. Radiology. 1990;175:745–52.
339. Reimche LD, Sankaran K, Hindmarsh KW, et al. Chloral hydrate sedation in neonates and infants – clinical and pharmacologic considerations. Dev Pharmacol Ther. 1989;12:57–64.
340. American Academy of Pediatrics Committee on Drugs and Committee on Environmental Health. Use of chloral hydrate for sedation in children. Pediatrics. 1993;92:471–3.
341. Rokicki W. Cardiac arrhythmia in a child after the usual dose of chloral hydrate. Pediatr Cardiol. 1996;17:419–20.
342. Seger D, Schwartz G. Chloral hydrate: a dangerous sedative for overdose patients? Pediatr Emerg Care. 1994;10:349–50.
343. D'Agostino J, Terndrup TE. Chloral hydrate versus midazolam for sedation of children for neuroimaging: a randomized clinical trial. Pediatr Emerg Care. 2000;16:1–4.
344. Collett BJ. Opioid tolerance: the clinical perspective. Br J Anaesth. 1998;81:58–68.
345. Finnegan LP. Effects of maternal opiate abuse on the newborn. Fed Proc. 1985;44:2314–7.
346. Finnegan LP, Connaughton Jr JF, Kron RE, et al. Neonatal abstinence syndrome: assessment and management. Addict Dis. 1975;2:141–58.
347. Arnold JH, Truog RD, Orav EJ, et al. Tolerance and dependence in neonates sedated with fentanyl

during extracorporeal membrane oxygenation. Anesthesiology. 1990;73:1136–40.
348. Arnold JH, Truog RD, Scavone JM, et al. Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. J Pediatr. 1991;119:639–43.
349. Tobias JD, Schleien CL, Haun SE. Methadone as treatment for iatrogenic opioid dependency in pediatric intensive care unit patients. Crit Care Med. 1990;18:1292–3.
350. Sury MRJ, Billingham I, Russell GN, et al. Acute benzodiazepine withdrawal syndrome after midazolam infusions in children. Crit Care Med. 1989;17:301–2.
351. van Engelen BGM, Gimbrere JS, Booy LH. Benzodiazepine withdrawal reaction in two children following discontinuation of sedation with midazolam. Ann Pharmacother. 1993;27:579–81.
352. Fonsmark L, Rasmussen YH, Carl P. Occurrence of withdrawal in critically ill sedated children. Crit Care Med. 1999;27:196–9.
353. Tobias JD, Deshpande JK, Pietsch JB, et al. Pentobarbital sedation for patients in the pediatric intensive care unit. South Med J. 1995;88:290–4.
354. Ho IK, Yamamoto I, Loh HH. A model for the rapid development of dispositional and functional tolerance to barbiturates. Eur J Pharmacol. 1975;30:164–71.
355. Jaffe JH, Sharpless SK. The rapid development of physical dependence on barbiturates. J Pharmacol Exp Ther. 1965;150:140–6.
356. Cammarano WB, Pittet JF, Weitz S, et al. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. Crit Care Med. 1998;26:676–84.
357. Imray JM, Hay A. Withdrawal syndrome after propofol. Anaesthesia. 1991;46:704–5.
358. Arnold JH, Truog RD, Molengraft JA. Tolerance to isoflurane during prolonged administration. Anesthesiology. 1993;78:985–8.
359. Hughes J, Leach HJ, Choonara I. Hallucinations on withdrawal of isoflurane used as sedation. Acta Paediatr. 1993;82:885–6.
360. Katz R, Kelly W, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. Crit Care Med. 1994;22:763–7.
361. Anand KJS, Arnold JH. Opioid tolerance and dependence in infants and children. Crit Care Med. 1994;22:334–42.
362. Ista E, van Dijk M, Gamet C, et al. Withdrawal symptoms in children after long-term administration of sedative and/or analgesics: a literature review. "Assessment remains troublesome". Intensive Care Med. 2007;33:1396–406.
363. Cunliffe M, McArthur L, Dooley F. Managing sedation withdrawal in children who undergo prolonged PICU admission after discharge to the ward. Pediatr Anesth. 2004;14:293–8.
364. Franck LS, Naughton I, Winter I. Opioid and benzodiazepine withdrawal symptoms in paediatric intensive care patients. Crit Care Nurs. 2004;20:344–51.
365. Ista E, van Dijk M, Gamel C, et al. Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: a first evaluation. Crit Care Med. 2008;36:2427–32.
366. Robertson RC, Darsey E, Fortenberry JD, et al. Evaluation of an opiate-weaning protocol using methadone in pediatric intensive care unit patients. Pediatr Crit Care Med. 2000;1:119–23.
367. Lugo RA, MacLaren R, Cash J, et al. Enteral methadone to expedite fentanyl discontinuation and prevent opioid abstinence syndrome in the PICU. Pharmacotherapy. 2001;21:1566–73.
368. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedative and analgesics in the critically ill adult. Crit Care Med. 2002;30:119–41.
369. Playfor S, Jenkins I, Boyles C, et al. A consensus guidelines on sedation and analgesia in critically ill children. Intensive Care Med. 2006;32:1125–36.
370. Tobias JD. Outpatient therapy of iatrogenic drug dependency following prolonged sedation in the pediatric intensive care unit. Intensive Care Med. 1996;11:284–7.
371. Meyer MT, Berens RJ. Efficacy of an enteral 10-day methadone wean to prevent opioid withdrawal in fentanyl-tolerant pediatric intensive care unit patients. Pediatr Crit Care Med. 2001;2:329–33.
372. Siddappa R, Fletcher JE, Heard AMB, et al. Methadone dosage for prevention of opioid withdrawal in children. Pediatr Anesth. 2003;13:805–10.
373. Berens RJ, Meyer MT, Mikhailov TA, et al. A prospective evaluation of opioid weaning in opioid-dependent pediatric critical care patients. Anesth Analg. 2006;102:1045–50.
374. Atkinson D, Dunne A, Parker M. Torsades de pointes and self-terminating ventricular fibrillation in a prescription methadone user. Anaesthesia. 2007;62:952–5.
375. Nathenson G, Golden GS, Litt IF. Diazepam in the management of the neonatal narcotic withdrawal syndrome. Pediatrics. 1971;48:523–7.
376. Kaltenbach K, Finnegan LP. Neonatal abstinence syndrome, pharmacotherapy, and developmental outcome. Neurobehav Toxicol Teratol. 1986;8:353–5.
377. Kron RE, Litt M, Eng D, et al. Neonatal narcotic abstinence: effects of pharmacotherapeutic agents and maternal drug usage on nutritive sucking behavior. J Pediatr. 1976;88:637–41.
378. Madden JD, Chappel JN, Zuspan F, et al. Observation and treatment of neonatal narcotic withdrawal. Am J Obstet Gynecol. 1989;127:199–201.
379. Kandall SR. Managing neonatal withdrawal. Drug Ther. 1976;6:47–59.
380. Cobrinik RW, Hood RTJ. The effect of maternal narcotic addiction on the newborn infant. Pediatrics. 1959;24:288–93.
381. Gold MS, Redmond Jr DER, Kleber HD. Clonidine blocks acute opiate-withdrawal symptoms. Lancet. 1978;222:599–602.

382. Hoder EL, Leckman JF, Ehrenkranz R, et al. Clonidine in neonatal narcotic-abstinence syndrome. N Engl J Med. 1981;305:1284–5.
383. Deutsche ES, Nadkarni VM. Clonidine prophylaxis for narcotic and sedative withdrawal syndrome following laryngotracheal reconstruction. Arch Otolaryngol Head Neck Surg. 1996;122: 1234–8.
384. Tobias JD. Subcutaneous dexmedetomidine infusions to treat or prevent drug withdrawal in infants and children. J Pain Symptom Manage. 2008;4:187–91.
385. Ely EW, Gautam S, Margolin R, Francis J, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med. 2001;27:1892–900.
386. Jackson JC, Gordon SM, Hart RP, et al. The association between delirium and cognitive decline: a review of the empirical literature. Neurophychol Rev. 2004;14:87–98.
387. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2009;291: 1753–62.
388. Ely EW, Stephens RK, Jackson JC, et al. Current opinions regarding the importance, diagnosis, and management of delirium in the intensive care unit: a survey of 912 healthcare professionals. Crit Care Med. 2004;32:106–12.
389. Meagher DJ, Trzepacz PT. Motoric subtypes of delirium. Semin Clin Neuropsychiatry. 2000;5:75–85.
390. Peterson JF, Pun BT, Dittus RS, Thomason JW, Jackson JC, Shintani AK, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. J Am Geriatr Soc. 2006;54:479–84.
391. Ouimet S, Riker R, Bergeon N, et al. Subsyndromal delirium in the ICU: evidence for a disease spectrum. Intensive Care Med. 2007;33:1007–13.
392. Spronk PE, Rickerk B, Hofhuis J, et al. Occurrence of delirium is severely underestimated in the ICU during daily care. Intensive Care Med. 2009;35: 1276–80.
393. Bergeron N, Dubois MJ, Dumont M, et al. Intensive care delirium screening checklist: evaluation of a new screening tool. Intensive Care Med. 2001;27:859–64.
394. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286:2703–10.
395. Ely EW, Girard TD, Shintani AK, et al. Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients. Crit Care Med. 2007;35:112–7.
396. Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. JAMA. 1994;272:1518–22.
397. Ouimet S, Kavanagh BP, Gottfried SB, et al. Incidence, risk factors and consequences of ICU delirium. Intensive Care Med. 2007;33:66–73.
398. Morrison RS, Magaziner J, Gilbert M, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci. 2003;58:76–81.
399. Tzepacz PT. Update on the neuropathogenesis of delirium. Dement Geriatr Cogn Disord. 1999;10: 330–4.
400. Tzepacz PT. Delirium. Advances in diagnosis, pathophysiology, and treatment. Psychiatr Clin North Am. 1996;19:429–48.
401. Van Der Mast RC. Pathophysiology of delirium. J Geriatr Psychiatry Neurol. 1998;11:138–45.
402. Wurtman RJ, Hefti F, Melamed E. Precursor control of neurotransmitter synthesis. Pharmacol Rev. 1980;32:315–35.
403. Krueger JM, Walter J, Dinarello CA, et al. Sleep-promoting effects of endogenous pyrogen (interleukin-1). Am J Physiol. 1984;246:R994–9.
404. Inouye SK, Bogardus Jr ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999;340: 669–76.
405. Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000;342:1471–7.
406. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc. 2005;53: 1658–66.
407. Skrobik YK, Bergeron N, Dumont M, et al. Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med. 2004;30:444–9.
408. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine versus midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301:489–99.