

Clinical Policy: Evidence-Based Approach to Pharmacologic Agents Used in Pediatric Sedation and Analgesia in the Emergency Department

From the EMSC Grant Panel (Writing Committee) on Pharmacologic Agents Used in Pediatric Sedation and Analgesia in the Emergency Department

Sharon E. Mace, MD, Chair, American College of Emergency Physicians (ACEP)
 Isabel A. Barata, MD (ACEP)
 Joseph P. Cravero, MD (American Society of Anesthesiologists)
 William C. Dalsey, MD (ACEP)
 Steven A. Godwin, MD (ACEP)
 Robert M. Kennedy, MD (American Academy of Pediatrics)
 Kelly C. Malley, CPNP, RN (Emergency Nurses Association)
 R. Lawrence Moss, MD (American Pediatric Surgical Association)
 Alfred D. Sacchetti, MD (ACEP)
 Craig R. Warden, MD, MPH (ACEP)
 Robert L. Wears, MD, MS, Methodologist (ACEP)

Other members of the EMSC Grant Panel included:

John A. Brennan, MD (ACEP Board Liaison)
 Rhonda R. Whitson, RHIA (Clinical Policies Manager, ACEP)
 Heather Crown, MRC (EMSC, Public Policy and Partnerships Specialist)
 Dan Kavanaugh, MSW (EMSC Program Director)
 Susan Eads Role, JD, MSLS (EMSC, Public Policy and Partnerships Director).

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INTRODUCTION

The appropriate management of pain and anxiety in the emergency department (ED) is a significant facet of emergency care for all patients, including pediatric patients. The administration of drugs for the purpose of reducing or eliminating pain and awareness or providing sedation is an essential component of emergency medicine practice and is a requirement of emergency medicine training programs.¹⁻³ Proactively addressing pain and anxiety may improve quality of care and patient satisfaction by facilitating interventional procedures and minimizing patient suffering.

Effective and safe procedural sedation requires the selection of appropriate drugs, given in appropriate doses, on selected patients, and in the proper environment. The logistics of procedural sedation in the ED and the hospital has been documented elsewhere.^{1,4} There are a variety of drugs available for use in procedural sedation and analgesia. Selection of a particular drug is dependent on many variables, including patient characteristics, the procedure to be performed, and clinician experience. For example, sedation of children with American Society of Anesthesiologists (ASA) status III or IV has been associated with a higher rate of oxygen desaturation and airway difficulties than children with ASA status I or II.⁵

This clinical policy focuses on the use of medications to achieve sedation and analgesia in pediatric patients undergoing procedures in the ED. Specific sedation and analgesia drugs focused on in this document are: etomidate, fentanyl/midazolam, ketamine, methohexital, pentobarbital, and propofol. These 6 drugs represent sedation and analgesia agents used in the ED.

Procedural sedation is defined as the technique of administering sedatives or dissociative agents with or

without analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function.¹ Procedural sedation is generally combined with analgesia to minimize pain whenever the procedure is uncomfortable or painful. The goal of procedural sedation and analgesia is to create a depressed level of consciousness while the patient concurrently maintains his or her own airway and oxygenation without assistance. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), the ASA, and the American Academy of Pediatrics (AAP) have defined the levels of sedation and analgesia.^{4,6,7}

Moderate sedation/analgesia, formerly “conscious sedation,” is a drug-induced depression of consciousness during which patients respond purposefully to verbal or light tactile stimulation while generally maintaining protective airway reflexes.^{4,7,8} Deep sedation/analgesia is a drug-induced depression of consciousness in which patients are not easily aroused and may need airway and ventilatory assistance, although they purposefully respond to repeated or painful stimulation.^{4,7,8} General anesthesia is a drug-induced loss of consciousness during which patients are not arousable and often have impaired cardiorespiratory function needing support.^{4,8} Because individuals vary in their response to medications, and sedation for analgesia is a continuum, the practitioner providing sedation and analgesia needs to be proficient in airway management and cardiovascular support.^{1,4,7,8} Guidelines for monitoring patients under moderate sedation, deep sedation, and anesthesia have been recommended.^{1,4,7,8} Furthermore, whenever moderate or deep sedation is given, the standards for anesthesia care are applicable.⁶

This policy is not intended to be all encompassing and is a guideline. It represents evidence for answering important questions about critical diagnostic and management issues. Recommendations in this policy are not intended to represent the only diagnostic and management options that the emergency physician can consider. The authors clearly recognize the importance of the individual physician’s judgment. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the critical questions addressed in this policy.

METHODOLOGY

This policy provides an evidence-based approach to pediatric procedural sedation and analgesia and was created after careful review and critical analysis of the peer-reviewed literature. Multiple MEDLINE searches

were done on each of the 6 drugs (etomidate, fentanyl/midazolam, ketamine, methohexital, pentobarbital, and propofol). The drug names were then combined with a search expression designed to identify adverse effects, apnea, vomiting/aspiration, laryngospasm, and hypotension. Finally, the results were limited to English-language studies published between 1966 and 2002 that examined human subjects aged 1 to 18 years. Variants on this search strategy, limiting results to clinical trials or to review articles, were also run.

Searches were done for pre-1966 articles by drug name and were limited to English-language studies; however, no studies from this search were selected for further scrutiny.

Several additional searches were done crossing specific drugs or drug combinations with the terms “conscious sedation” or “procedural sedation” or “procedures.” A search of other relevant materials, such as textbooks and reference databases, identified 3 additional papers that were not indexed by drug name. A final set of searches was performed that did not use any specific drug names, but was limited to publication dates from 1966 to 2002, human subjects, subjects aged 1 to 18 years, and conscious sedation or pediatric sedation. A manual search was performed in the peer-reviewed emergency medicine literature for pertinent articles published in 2003.

References obtained on the searches were reviewed by panel members (title and abstract, where available) for relevance before inclusion in the pool of studies to be reviewed. Abstracts and articles were reviewed by subcommittee members, and pertinent articles were selected. These articles were evaluated, and those addressing the questions considered in this document were chosen for grading. Subcommittee members also supplied references from bibliographies of initially selected articles or from their own files.

All publications were graded by at least 2 of the subcommittee members into 1 of 3 categories of strength of evidence. Some articles were downgraded on the basis of a standardized formula that considers the size, age, and location of the study population, methodology, validity of conclusions, and potential sources of bias (Appendix A).

During the review process, all articles were given a baseline “strength of evidence” by the subcommittee members according to the following criteria:

Strength of evidence Class I—Interventional studies including clinical trials, observational studies including prospective cohort studies, aggregate studies including meta-analyses of randomized clinical trials only.

Strength of evidence Class II—Observational studies including retrospective cohort studies, case-controlled

studies, aggregate studies including other meta-analyses.

Strength of evidence Class III—Descriptive cross-sectional studies, observational reports including case series and case reports, consensus studies including published panel consensus by acknowledged groups of experts.

Strength of evidence Class I and II articles were then rated on elements the subcommittee members believed were most important in creating a quality work. Class I and II articles with significant flaws or design bias were downgraded on the basis of a set formula (Appendix B). Strength of evidence Class III articles were downgraded if they demonstrated significant flaws or bias. Articles downgraded below strength of evidence Class III were given an “X” rating and were not used in formulating recommendations in this policy. An **Evidentiary Table** was constructed and is included at the end of this policy.

Most of the studies included in this guideline lacked a standardized validated scoring system for evaluation of efficacy. In addition, the endpoints differed among the various studies. For many studies, efficacy was defined as the completion of the procedure without any measurement of the degree of sedation. When this occurred, the panel noted “efficacy was not addressed.” When a success/failure rate was given, efficacy was graded as Class III. When there was a quantitative measure of sedation, efficacy was given a higher grade (Class I or II) depending on the overall assessment.

In considering the question of safety with respect to the administration of the various drugs included in this clinical policy, the panel recognized that there is not sufficient power in the peer-reviewed literature to document true “safety” for any of the agents involved in any setting, including the operating suite, because critical incidents of very low frequency would require patient cohorts of thousands to be fully evaluated. Lacking this type of data, the panel considered all of the available information from studies that took place in an ED or analogous venue and graded safety on the basis of the available data. More conclusive statements concerning the safety of pediatric sedation with respect to specific agents will await future studies.

Recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on strength of evidence Class

I or overwhelming evidence from strength of evidence Class II studies that directly address all the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on strength of evidence Class II studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of strength of evidence Class III studies).

Level C recommendations. Other strategies for patient management based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, strength of prior beliefs, and publication bias, among others, might lead to such a downgrading of recommendations.

Expert review comments were received on an earlier draft of this document from members of the AAP, the American Pediatric Surgical Association, the ASA, the Emergency Nurses Association, and the American College of Emergency Physicians. Their responses were used to further refine and enhance this policy.

Scope of Application. This policy is intended for physicians administering procedural sedation and analgesia to pediatric patients in hospital-based EDs.

Inclusion Criteria. This policy applies to patients between the ages of 1 to 18 years who are in a hospital ED and have conditions necessitating the alleviation of anxiety, pain, or both.

Exclusion Criteria. This policy excludes: (1) children younger than 1 year, (2) patients receiving analgesia to treat pain without concomitant sedative use, (3) intubated patients, and (4) inhalational anesthetics.

CRITICAL QUESTIONS

Etomidate

Etomidate is an imidazole derivative that acts as a hypnotic without analgesic properties and has a favorable hemodynamic profile in both adults and children.⁹⁻¹¹ There are limited data available on the use of etomidate in procedural sedation.

There were 56 articles reviewed. The articles that described the use of etomidate for procedural sedation in a setting compatible to the ED were then included. A total

of 4 ED-based studies were included. In addition, 4 studies evaluating the presence of adrenal suppression and 3 studies looking at myoclonus and/or pain with injection in patients receiving etomidate were included.

I. Is etomidate effective for providing procedural sedation in children in the ED?

Four recent studies have been published regarding the performance of etomidate as a procedural agent specifically in the ED. The literature does not clearly address the need for the use of analgesia with etomidate, thus no recommendation can be made in this document. In a retrospective review of 53 children (25 <10 years), Dickinson et al¹² described the drug's use in the reduction of pediatric orthopedic procedures. The authors found an 83% procedural success rate after the first attempt. After an initial retrospective pilot study of 9 patients, Ruth et al¹³ designed a descriptive, prospective feasibility study that specifically evaluated complications arising from intravenous etomidate in 51 patients. Physician assessments reported a 98% (59/60) satisfaction with adequate sedation. This study included only 18 children aged 5 to 18 years with the predominance of pediatric sedation performed for fracture reduction. The authors reported that 98% (50/51) of the patients reached adequate sedation, and procedural success was reported in 92% (47/51) of the patients. In a retrospective observational study performed by Vinson and Bradbury¹⁴ of 150 procedures, 11% (15/134) of patients enrolled were children aged 6 to 17 years. Moderate sedation was documented in 32% (48/150) of the procedures, and deep sedation was induced in 68% (102/150) of the procedures as measured by the Aldrete Postanesthetic Recovery Score. The authors reported that 11% (16/150) of the procedures required additional doses of medication to complete the procedure, with 9% (13/150) receiving 2 doses and 2% (3/150) requiring 3 doses. These results are complicated by the 23% (34/150) of procedures that used adjunctive medications including opiates, benzodiazepines, or both. In the 113 patients receiving etomidate only, the authors could identify no proportional increase in depth and duration of sedation with increasing mean etomidate doses.

Another smaller retrospective chart review of 46 adults and 2 children identified 8.3% (4/48) of patients with procedural failure.¹⁵ Each of the retrospective studies have been criticized because of the inherent flaws associated with their incomplete data sets.

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Etomidate is an effective agent for procedural sedation in the pediatric patient population within the ED.

II. Is etomidate safe for providing procedural sedation in children in the ED?

Dickinson et al¹² documented side effects including 0.7% (1/153) of patients with nausea and 0.7% (1/153) of patients requiring a fluid bolus for transient hypotension. There were no reported incidences of patients who required assisted ventilation of any kind. Adverse events captured by Ruth et al¹³ included brief desaturations requiring face-mask oxygen supplementation in 9.8% (5/51), myoclonus in 7.8% (4/51), vomiting in 1.9% (1/51), pain with injection in 1.9% (1/51), and a less than 30-second episode of desaturation-induced bradycardia that was "immediately" corrected with face-mask oxygen supplementation in 1.9% (1/51). The authors fail to further describe the pediatric age distribution, and no specific pediatric issues received comment. Vinson and Bradbury¹⁴ described oxygen desaturation in 5 adults (N=150; 3.3%) that was treated with face-mask oxygen supplementation. Of these 5 patients, 4 (N=150; 2.7%) also received bag-assisted ventilation. The 5 patients needing supplemental face-mask oxygen all received higher doses of etomidate (0.23 mg/kg) and were older than 55 years; 2 (N=150; 1.3%) patients had emesis. A follow-up questionnaire revealed that 95% (114/120) of responders stated they would be "extremely" willing to have etomidate again. Keim et al¹⁵ found 21% (10/48) of patients with adverse reactions. Respiratory complications occurred in 4% (2/48) of patients, with 1 patient developing transient apnea requiring bag-valve-mask ventilation, whereas another patient required a nonrebreather mask for oxygen desaturation below 90%. In addition, 4% (2/48) of patients developed emesis, and procedure failure was documented in 8% (4/48) of patients.

In a study by McDowell et al,¹⁶ the etomidate group was associated with more episodes of vomiting (9.9%; 10/101) and agitation (4%; 4/101) compared with 603 reviewed charts of patients receiving propofol (0.5% [3] and 1.2% [7], respectively). The etomidate group did experience significantly less hypoxia (oxygen saturation <94%; 2% [2/101]) than the propofol group (15.7% [95/603]). Myoclonus was also noted in 18% (18/101) of the etomidate group.

Although trials investigating etomidate-induced adrenal suppression in procedural sedation are not available, numerous studies have demonstrated cortisol depression for up to 24 hours with as little as a single dose of etomidate. However, the levels consistently remain in the normal range with no clinically significant sequelae.¹⁷⁻²⁰

Pain with injection and myoclonus are also commonly reported side effects associated with etomidate.^{13,16,21} Pain with injection occurred in 1.9% (1/51) of patients in the study by Ruth et al¹³ (patients were also given analgesics), and in 17% (5/29) of patients in the study by Helmers et al.²¹ Myoclonus was noted in 7.8% (4/51),¹³ 17.8% (18/101) (versus 0% [0/267] for ketamine and 0% [0/603] for propofol),¹⁶ and 37.9% (11/29)²¹ of patients. When present, myoclonus usually lasts less than 1 minute but can resemble seizure activity and can be decreased by the coadministration of other drugs. These tremors are benign and not epileptiform activity.^{21,22}

One study has evaluated etomidate's ability to induce electroencephalogram burst suppression to facilitate intubation in the presence of increased intracranial pressure. A significant reduction in intracranial pressure was observed during tracheal manipulation, with minimal effects on cerebral perfusion pressure.²²

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Etomidate is a safe agent for procedural sedation in the pediatric patient population within the ED.

Fentanyl/Midazolam

Fentanyl is an opiate that is 100 times more potent than morphine. Opiates are powerful analgesics that also produce varying amounts of sedation and reduce anxiety through direct action on opiate receptors.⁹ Fentanyl is active within 2 to 3 minutes of intravenous administration, with a duration of action of 20 to 30 minutes.²³

Midazolam is a short-acting benzodiazepine. Benzodiazepines produce sedation, anxiolysis, and anterograde amnesia through direct action on a benzodiazepine receptor. Benzodiazepines have no analgesic properties. Midazolam is active within 2 to 3 minutes of intravenous administration, with a duration of approximately 30 minutes.²⁴

Twenty-eight articles concerning the parenteral use of fentanyl and midazolam were reviewed. After grading, 14 articles were included in this analysis. These articles

include several ED-based clinical studies and some studies involving only adults.

III. Are fentanyl and midazolam effective for providing procedural sedation in children in the ED?

Fentanyl and midazolam are widely used and effective agents for sedation and analgesia in the pediatric population. The efficacy of intravenous fentanyl and midazolam is reported to be high, ranging from 91% to 100%.²⁵⁻²⁸ It has been found to be of similar efficacy when compared with alternative agents. The analgesic and sedative effects of fentanyl may be increased when combined with a benzodiazepine.²⁹

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Intravenous use of fentanyl and midazolam is effective for pediatric sedation during painful procedures in the ED.

Level C recommendations. None specified.

IV. Is the use of fentanyl and midazolam safe for providing procedural sedation for painful procedures in children in the ED?

The primary adverse effect of opiates is respiratory depression and resultant hypoxia and/or apnea. Additional side effects include nausea, vomiting, and pruritis.

In rare cases, chest wall rigidity, in addition to hypoxia from respiratory depression, is reported when fentanyl is given in moderate-to-large doses or with rapid administration.³⁰ The effects of fentanyl may be reversed with naloxone or naltrexone.³¹

The primary adverse effects of midazolam are respiratory depression, paradoxical excitement, and occasional hypotension.³² The effects of midazolam may be reversed by flumazenil.

The use of opiates and benzodiazepines together is widely reported to produce a synergistic response of both the desired effects and adverse side effects.³³ In 2 adult studies, the risk of respiratory depression and apnea was increased (92% versus 50% and 63% versus 3%) when fentanyl was administered in conjunction with midazolam.^{34,35} The strong respiratory depressant effect of the fentanyl and midazolam combination was further underscored by McQuillen and Steele³¹ and Kennedy et al,²⁹ who both reported an increased risk of respiratory depression. However, 2 retrospective case series refute the assertion that fentanyl and midazolam in combination are more dangerous than either agent alone.^{24,32} Two randomized trials did not find a significantly increased risk for fentanyl

and midazolam in combination, but both of these studies were very small.^{25,26} In Pena and Krauss²³ large prospective series of 1,180 patients, the authors found no increased risk of respiratory depression with fentanyl and midazolam compared with other agents. The disparity in these findings may be related to the method used to assess respiratory depression or monitor for serious adverse events. Most studies report very low incidences of apnea or serious adverse events (0% to 2%), with much higher frequencies of decreased pulse oximetry or increases in end-tidal carbon dioxide (ETCO₂). When these occurred, the patients usually responded to verbal stimulation, repositioning, or other minor interventions. Rarely did patients require bag-valve-mask ventilation or intubation.

The incidence of serious respiratory events is quite low for pediatric sedation with fentanyl and midazolam. Of 334 patients reported by Graff et al,³² 11% had minor respiratory events and 2 required naloxone. No patients required ventilatory assistance. Hostetler and Barnard³³ reported transient hypoxia in 15% of 28 children receiving fentanyl and midazolam and no life-threatening events. Other reports similarly found that approximately 10% to 20% of patients had a mild respiratory event requiring oxygen or stimulation, while the need for respiratory assistance was rare, and the incidence of life-threatening events was near zero.^{23,26,29,32} One case report of a respiratory arrest in an unmonitored 13-month-old child receiving fentanyl and midazolam serves as a reminder that these drugs do have potentially life-threatening consequences and that close monitoring and emergency backup measures are essential.³⁶

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. The combination of fentanyl and midazolam appears to result in a greater risk of respiratory depression; therefore, the clinician should take particular care to monitor the patient for signs of respiratory depression and should have appropriate training and support to treat apnea.

Level C recommendations. None specified.

Ketamine

Ketamine is a sedative-analgesic medication for procedural sedation.⁹ It has a unique mechanism of action based on N-methyl-D-aspartate glutamate receptor antagonism and is classified as a dissociative agent allowing potent sedation, analgesia, and amnesia during painful

procedures. Onset of sedation-analgesia is rapid by either intravenous or intramuscular administration. Twenty-nine articles concerning the parenteral use of ketamine in an ED were reviewed. After grading, 19 articles were included in this analysis. There were no ED-based studies of ketamine for imaging sedation.

V. Is ketamine effective for providing procedural sedation in children in the ED?

A partially blinded, randomized, controlled trial of intravenous propofol/fentanyl (1 mg/kg initially with smaller aliquots and 1 to 2 µg/kg aliquots, respectively) versus ketamine/midazolam (1 to 2 mg/kg and 0.05 mg/kg aliquots, respectively) for orthopedic procedural sedation in children aged 3 to 18 years showed ketamine/midazolam to have statistically better but questionable clinical significance, improved Observation Score of Behavioral Distress–Revised (OSBD-R) scores during manipulation (0.278 versus 0.084 [Δ 0.194; 95% confidence interval (CI) 0.048 to 0.340; $P=$.008]), and equivalent orthopedic, nursing, and parental satisfaction scores.³⁷ Intravenous ketamine/midazolam (1 mg/kg and 0.1 mg/kg, respectively) was superior to intranasal midazolam (0.5 mg/kg) in patients undergoing laceration repair for sedation onset and consistency of effect. At 30 minutes, the average sedation score was 2.4 versus 3.5 ($P<$.001), and the average sedation visual analog scale (VAS) score was 1.8 versus 3.8 ($P<$.001). Physician and parental satisfaction was rated “excellent or good” in 88% versus 54% ($P=$.006) and 92% versus 65% ($P=$.02), respectively.³⁸ Intramuscular ketamine (4 mg/kg) was superior to intramuscular meperidine/promethazine/chlorpromazine in a study of patients undergoing wound repair, burn care, or lumbar puncture, demonstrating a mean OSBD-R score of 2.7 versus 9.8 ($P<$.003).³⁹ Ketamine/midazolam was superior to fentanyl/midazolam for procedural sedation for orthopedic procedures demonstrating a mean OSBD-R score of 1.12 versus 2.70 ($P\leq$.0001).²⁹ In these 3 Class I studies, the efficacy of ketamine for “adequacy of sedation” to complete the procedure was 100%.

Low-dose intramuscular ketamine (2.5 mg/kg) was shown to be superior to intranasal midazolam in laceration repair: 100% versus 70% were rated as “cooperative” or “intermittently crying” during repair ($P<$.01).⁴⁰ Several prospectively designed, single treatment arm studies have also shown that ketamine has a high efficacy rate and high provider and parental satisfaction.⁴¹⁻⁴³ (See [Evidentiary Table](#) for comparisons.)

Patient Management Recommendations

Level A recommendations. Ketamine is effective either as a sole agent or in combination with a benzodiazepine for brief painful procedures in children.

Level B recommendations. None specified.

Level C recommendations. None specified.

VI. Is ketamine safe for providing procedural sedation in children in the ED?

Two Class I studies for safety, either comparing ketamine/midazolam to fentanyl/midazolam or ketamine with or without midazolam, have demonstrated a good safety profile for ketamine in procedural sedation in children.^{29,44} Kennedy et al²⁹ found that, for ketamine/midazolam versus fentanyl/midazolam, in 260 cases patients had an incidence of hypoxemia of 6% versus 24% during sedation ($P=.001$), required breathing cues 1% versus 12% of the time ($P=.001$), required an airway maneuver 6% versus 11% of the time ($P=NS$), and required bag-valve-mask ventilatory support 2% versus 0% of the time ($P=NS$). A small pilot study of 20 pediatric patients undergoing ketamine sedation and using sidestream $ETCO_2$ monitoring demonstrated no evidence of hypoventilation.⁴⁵ In a study of 266 sedations, of which 137 received midazolam, Wathen et al⁴⁴ found that the rates of adverse effects in the ketamine versus ketamine/midazolam groups of recovery agitation were 7.1% versus 6.2% ($\Delta 0.8$ [95% CI -5.3 to 7.0]); SpO_2 less than 90% in 1.6% versus 7.3% ($\Delta -5.7\%$ [95% CI -5.7% to -0.9%]); and emesis in 19.4% versus 9.6% ($\Delta 9.8\%$ [95% CI 1.4% to 18.2%]). For patients older than 10 years, recovery agitation was 5.7% versus 35.7% ($\Delta -30.0\%$ [95% CI -49.3% to -10.7%]). Several large and moderate-sized Class II studies confirm that ketamine is very safe when used with adequate monitoring and resuscitation equipment for procedural sedation in children in the ED. There was no evidence of clinically evident aspiration in any of these studies.^{23,37,38,40-43,46-52} Specifically, the incidence of laryngospasm is very low: 1/108 (0.9%) in 1 prospective cohort study⁵² and 1.4% in a large (1,022 patients) retrospective cohort study.⁵⁰ However, a study of pediatric patients undergoing gastroenterology procedures (generally, esophagogastroduodenoscopy and/or colonoscopy) performed in a gastroenterology suite or in the pediatric ICU found transient laryngospasms occurred in 8.2% of patients. The only predictor of laryngospasm was decreasing age (13.9% in children <6 years versus 3.6% in children ≥ 6 years). Nearly half the patients in this study were ASA status III or greater.⁵³

Of note, despite some concern for the use of ketamine for sedation for procedures involving the oropharyngeal

and upper aerodigestive tract, several studies have evaluated this issue. A retrospective, uncontrolled comparison in esophageal foreign body removal using ketamine/midazolam versus fentanyl/midazolam showed hypoxemia in 10.7% (95% CI 6.6% to 14.8%) versus 15.4% (95% CI 8.6% to 22.2%) of patients; stridor in 1.8% (95% CI 0% to 3.6%) versus 0% (95% CI 0% to 1.9%) of patients; and bag-valve-mask ventilatory support in 3.6% (95% CI 1.1% to 6.1%) versus 3.8% (95% CI 0.2% to 7.4%) of patients.³³ Another prospective, nonrandomized study of intramuscular ketamine/midazolam for dental procedural sedations in the ED showed SpO_2 greater than 96% and no adverse airway events in all patients, and emesis in only 2 (4.8%) patients.⁴³

Patient Management Recommendations

Level A recommendations. Ketamine can be safely used for procedural sedation in children in the ED, but may require head positioning, supplemental oxygen, occasional bag-valve-mask ventilatory support, and measures to address laryngospasm.

Level B recommendations. None specified.

Level C recommendations. None specified.

VII. Does the addition of midazolam as an adjunct to ketamine for procedural sedation for children in the ED reduce recovery agitation or vomiting?

In many centers, ketamine is administered along with a benzodiazepine (usually midazolam) to reduce the incidence of unpleasant recovery agitation, hallucinations, or "bad dreams."

Two Class I studies have shown that midazolam does not decrease the incidence of recovery agitation when used with ketamine. Wathen et al⁴⁴ found that the incidence of recovery agitation in the ketamine versus ketamine/midazolam groups was 7.1% versus 6.2% ($\Delta 0.8$ [95% CI -5.3% to 7.0%]). In addition, in the age group greater than 10 years of age, the incidence of recovery agitation was increased in the ketamine/midazolam group 5.7% versus 35.7% ($\Delta -30.0\%$ [95% CI -49.3% to -10.7%]). The incidence of emesis was decreased in the ketamine/midazolam group: 19.4% versus 9.6% ($\Delta 9.8\%$ [95% CI 1.4% to 18.2%]). Sherwin et al⁴⁶ demonstrated no difference between the ketamine and ketamine/midazolam treatment groups in the incidence of recovery agitation (VAS 5 mm [interquartile range 3 mm to 14 mm] versus 4 mm [interquartile range 2 mm to 19 mm]; $P=.70$), and the incidence of emesis 12% versus 2% ($\Delta -10\%$ [95% CI -20% to 0%]; $P=.058$).

Patient Management Recommendations

Level A recommendations. The addition of midazolam as an adjunct to ketamine for procedural sedation for children in the ED does not decrease the incidence of emergent reactions.

Level B recommendations. The addition of midazolam as an adjunct to ketamine for procedural sedation for children decreases the incidence of emesis.

Level C recommendations. None specified.

Methohexital

Methohexital is a rapid-acting barbiturate that produces its effect through direct stimulation of the gamma-aminobutyric acid receptor.⁹ As a barbiturate, methohexital may be described as a pure sedative. As such, most of its applications are for sedation for painless diagnostic studies. A review of methohexital use in pediatric patients for procedural sedation was performed. A total of 50 articles were reviewed; however, only articles describing methohexital use for procedural sedation compatible to ED practice were included in the analysis. Those articles describing methohexital effectiveness as part of an induction process for general anesthesia in the operating room were excluded from analysis except for a single study describing only the hemodynamic parameters in children after a rectal dose commonly used in the ED. There were 6 articles selected for inclusion in this analysis.

VIII. Is methohexital effective for providing procedural sedation in children in the ED?

In all but 1 of the studies, the patients underwent sedation with methohexital for computed tomography (CT) or magnetic resonance imaging (MRI) scan studies.⁵⁴⁻⁵⁸ In the remaining study, the patients underwent oncology-related procedures such as lumbar punctures, in which local anesthesia was used.⁵⁹

Three different routes were described for methohexital administration (ie, intravenous, intramuscular, rectal) for CT scans.⁵⁴⁻⁵⁹ For all of the studies examining use for CT or MRI sedation, methohexital demonstrated efficacy from 92% to 100% as determined by cooperation with study and quality of study obtained.⁵⁶⁻⁵⁹ For the intravenous route, Class II and Class III data exist supporting efficacy of 99% to 100% for methohexital as determined by the ability to complete either CT studies or hematology/oncology procedures.^{57,59} For the intramuscular routes, a single Class II study documented 92% efficacy for ability to complete CT scan.⁵⁸ For rectal administration, a single Class I study demonstrated 95% efficacy.⁵⁶ Efficacy was defined on 2 separate 3-point scales, 1 examining the need for restraint and the other

motion artifacts on the CT scan. Doses of methohexital described included 1 mg/kg intravenously, 10 mg/kg intramuscularly, and 25 mg/kg rectally.

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Methohexital administered by either the intravenous, intramuscular, or rectal routes can provide effective sedation for children undergoing painless diagnostic studies.

Level C recommendations. None specified.

IX. Is methohexital safe for providing procedural sedation in children in the ED?

As a barbiturate, methohexital has the potential to produce hypotension, hypoventilation, and apnea in children in whom it is administered.⁵⁴⁻⁵⁹ Safety documentation was demonstrated through prospective monitoring of children undergoing sedation with methohexital. Continuous cardiac monitoring, pulse oximetry, and intermittent blood pressure monitoring were all used to document the safety of this medication.

Regardless of the route of administration, methohexital has the capacity to produce hypoventilation leading to hypoxia. The incidence of hypoxia with methohexital ranged from 1% to 6%.^{55-57,59} In all but 1 of the studies, the hypoxia was resolved through repositioning of the patient or administration of supplemental oxygen.⁵⁵⁻⁵⁷ In the only grade I study, 3 out of 100 patients required bag-valve-mask ventilation support, although this was performed as required by a sedation protocol and not at the discretion of the managing clinician.⁵⁶ No child demonstrated adverse effects from the hypoxia, and none required endotracheal intubation. Transient hypotension was noted in up to 17% of 1 group of patients when administered intravenously.⁵⁹ When studied echocardiographically, rectal administration was found to produce clinically insignificant hemodynamic effects.⁵⁴

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Methohexital can be safely used for procedural sedation but may require head positioning, supplemental oxygen, and occasional bag-valve-mask ventilatory support.

Level C recommendations. None specified.

Pentobarbital

Pentobarbital is a short-acting barbiturate used to facilitate obtaining diagnostic studies such as CT and MRI

scans of children.⁹ Barbiturates function at the gamma-aminobutyric acid receptor complex and produce a central nervous system depressant effect. Pentobarbital is a pure sedative agent. There were 14 articles reviewed and 11 studies included for this analysis. Most studies were done in fasted patients undergoing painless, diagnostic procedures.

X. Is pentobarbital effective for providing procedural sedation in children in the ED?

In the 11 studies included, pentobarbital was given intravenously, except in 1 study in which it was given orally.⁶⁰ Greenberg et al,⁶¹ using 6 mg/kg of pentobarbital divided in 3 doses to a maximum of 200 mg, found that 8% (8 children out of 100) of patients were not successfully sedated (were unable to complete their diagnostic study). The children who were not successfully sedated were either 12 years or older (characteristics of older children that required sedation were not defined in this article) or weighed greater than 50 kg, which may reflect the 200-mg maximum dose in this study. Best results were seen in children younger than 8 years.

When using pentobarbital for pediatric sedation, higher success rates of 99% or greater were found by Karian et al,⁶² Mason et al,⁶³ and Strain et al.⁶⁴

Mason et al,⁶³ in a nonblinded prospective study of 1,070 children, compared the use of intravenous pentobarbital alone and a combination of pentobarbital and midazolam and found no beneficial effect by adding midazolam. The success rate of the pentobarbital alone group was 99.5% compared with 99.8% in the pentobarbital-midazolam group. The use of midazolam increased time to sedation (pentobarbital-midazolam 8.0 ± 4.4 minutes versus pentobarbital 6.5 ± 4.4 minutes) and also prolonged the time to discharge by approximately 14 minutes when used in conjunction with pentobarbital (pentobarbital-midazolam 120 ± 32 minutes versus pentobarbital 106 ± 34 minutes).

Moro-Sutherland et al⁶⁵ compared the efficacy of intravenous midazolam to intravenous pentobarbital when used for sedation of 55 pediatric patients undergoing CT imaging of the head in the ED and found that pentobarbital had a 97% success rate compared with a 19% success rate for midazolam.

In a study by Kain et al⁶⁶ of 58 pediatric patients, group 1 received 1 to 2 mg/kg of propofol followed by propofol infusion, and group 2 received 1 to 3 mg/kg of thiopental followed by a 2- to 3-mg/kg pentobarbital bolus and supplemental doses of 1 to 2 mg/kg of thiopental were administered to maintain sedation. Time to recovery in

group 1 was 19 ± 7 minutes versus 35 ± 20 minutes in group 2. Time to discharge in group 1 was 24 ± 6 minutes versus 40 ± 11 minutes in group 2. Pentobarbital had a greater recovery time and longer time to discharge than propofol; however, adverse reactions were not addressed in this study.

Rooks et al,⁶⁰ in a study of 675 pediatric patients, compared the use of oral pentobarbital at an average dose of 4 mg/kg to oral chloral hydrate at an average dose of 50 mg/kg and found similar time to sedation (pentobarbital 19 ± 14 minutes and chloral hydrate 16 ± 11 minutes), time to discharge (pentobarbital 100 ± 35 minutes and chloral hydrate 103 ± 36 minutes), length of sedation (pentobarbital 81 ± 34 minutes and chloral hydrate 81 ± 34 minutes), and adverse reactions in both groups (pentobarbital 1.6% and chloral hydrate 1.7%). Adverse reactions were reported in 5 (1.6%) patients in the oral pentobarbital group versus 6 (1.7%) patients in the chloral hydrate group. In the pentobarbital group, 1 patient vomited after the second dose of pentobarbital, 1 patient who received 6 mg/kg had prolonged sedation with discharge after 5 hours, 1 patient had decrease in oxygen saturation level (patient had a history of severe gastroesophageal reflux) and required suctioning and airway repositioning, 1 patient had inspiratory and expiratory wheezing and responded to albuterol (patient had pre-existing respiratory condition), and 1 patient had a paradoxical reaction. One delayed event occurred in the oral pentobarbital group 4 hours after discharge when the patient had an episode of perioral cyanosis and was observed in the ED for 4 hours and discharged. In the chloral hydrate group, there were 4 patients with mild decrease in oxygen saturation. Of these 4, 2 patients required airway repositioning and 1 required bag-valve-mask ventilation. Other adverse reactions included irritability and hyperactivity lasting 30 minutes, and 1 episode of vomiting.

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Pentobarbital alone is effective in producing cooperation for painless diagnostic procedures. Best sedation results are seen in children younger than 8 years.

Level C recommendations. None specified.

XI. Is pentobarbital safe for providing procedural sedation in children in the ED?

Transient respiratory depression to oxygen saturation less than 10% below the baseline has been reported from

1.2% to 7.5% of pediatric patients undergoing sedation with pentobarbital, although in most cases oxygen desaturation responded to interventions such as head positioning or supplemental oxygen.^{60-64,67,68}

In a study by Sanderson⁶⁹ using a pentobarbital average dose of 4.6 mg/kg, there was a 14% rate of complications, including desaturation, vomiting, increased airway secretions, airway obstruction, coughing, and bronchospasm.

Emergence reactions were documented in 4 separate studies.^{60,61,63,68} Hyperactivity was noted by Slovis et al⁶⁰ and Greenberg et al⁶¹ in 5% (17/357) to 7% (7/100) of children sedated with pentobarbital. Slovis et al⁶⁰ also reported an even higher rate of 8.4% in children older than 8 years. However, Greenberg et al⁶¹ noted that this only led to sedation failure in 1 child out of 100. Rooks et al⁶⁰ and Mason et al⁶³ described a paradoxical reaction as a patient experiencing sustained inconsolability and severe irritability and combativeness for more than 30 minutes after the administration of pentobarbital or after awakening from the sedation. A paradoxical reaction occurred in less than 0.01% (1/317) of children in the oral pentobarbital group in the study by Rooks et al,⁶⁰ and in 1.5% (10/640) of children in the intravenous pentobarbital group in the study by Mason et al.⁶³ Emesis was reported in 0.53% to 1% of the patients.^{61,63,67} One study reported a 3% incidence of coughing that led to a 1% failure rate.⁶¹

The duration of action is variable, the average induction time is 6 minutes, and the duration of sedation is up to 106 minutes, but most patients are alert within 30 to 60 minutes of administration.^{63,65} Greenberg et al⁶¹ found a 2% prolonged sedation rate of greater than 120 minutes when the maximum suggested dose was exceeded.

Slovis et al⁶⁰ performed a 24-hour follow-up of pediatric patients aged 12 months and older who had been sedated for MRI by using 3 mg/kg of pentobarbital alone or followed by 1 µg/kg of fentanyl if the patient was not asleep 5 minutes after the administration of pentobarbital; the study found that 19% of children slept for more than 8 hours. The multiple-dose regimen of pentobarbital had a significant short-term effect on children aged younger than 8 years, with 35% sleeping longer than 8 hours after the MRI.

Bloomfield et al⁷⁰ found greater recovery time (range 0 to 67 minutes) for pentobarbital compared with propofol (range 1 to 18 minutes); however, the pentobarbital group had fewer adverse reactions, less decrease in pulse rate, and less transient decrease in oxygen saturation than propofol.

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Pentobarbital can be safely used for procedural sedation but may require head positioning, supplemental oxygen, and occasional bag-valve-mask ventilatory support.

Level C recommendations. None specified.

Propofol

Propofol is a highly lipid-soluble alkyl phenol sedative agent.⁹ Operating through an interaction with the gamma-aminobutyric acid receptor system, propofol is proposed to prolong the duration of contact between gamma-aminobutyric acid and its receptor site. This action promotes an extended chloride influx into the neuron, leading to hyperpolarization of the neuronal cell membrane.⁷¹

Propofol is classified as a pure sedative. Unlike other pure sedatives, because of its potency propofol has been used for both painful and painless procedures. For painless diagnostic studies such as MRI or CT scans, propofol is generally used alone. For painful procedures, it is frequently combined with a short-acting potent opiate analgesic, although it has been used alone for painful procedures.^{37,72}

A total of 63 articles were reviewed; however, only articles describing propofol use for procedural sedation compatible to ED practice were included in the analysis. Although propofol has an extensive history of safe and effective use in general anesthesia, articles describing its use as an induction agent in the operating room or in combination with inhalation agents were not selected. Articles describing propofol's use for brief procedures, such as lumbar puncture for intrathecal medications or bone marrow biopsies, were included. Although these are not necessarily ED procedures, the manner in which propofol was used to facilitate a brief painful activity was considered consistent with how the drug may be used in the ED. There were 14 articles selected for inclusion in the analysis.

XII. Is propofol effective for providing procedural sedation in children in the ED?

In all instances, propofol was administered intravenously. For short procedures, propofol was administered as a bolus followed by additional doses as needed to maintain cooperation.^{37,73-76} For longer procedures, propofol treatment was initiated with an intravenous bolus, with sedation maintained through a continuous infusion.^{66,70,72,77-82}

Of the studies included in the analysis, 12 described propofol's efficacy in providing cooperation for an intended procedure. One study with Class I and 1 with Class III evidence used the 6-point Ramsay scoring system in documenting propofol's efficacy.^{72,82} In these studies, propofol produced mean sedation levels of 5.5⁷² and 5.6.⁸² In 1 of these studies, propofol was paired with a fixed dose of an opiate.⁷² A second study with Class I evidence again combined propofol with an opiate but used the OSBD-R scoring system to rate the efficacy of this combination for orthopedic procedures.³⁷ Propofol's sedation score was 0.278 in this system, in which a score of 0 represents no distress, whereas 23.5 represents maximal distress. Another study with Class II evidence used radiologists' objective assessments of lack of motion artifacts in MRI scans and showed good efficacy for children sedated with propofol, with mean quality scores of 9.0 out of 10.⁶⁶

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Propofol combined with opiate agents is effective in producing cooperation for painful therapeutic or diagnostic studies.

Level C recommendations. Propofol alone, without the concomitant use of opiate agents, is likely to be effective in producing sedation for painless diagnostic studies in ED patients.

XIII. Is propofol safe for providing procedural sedation in children in the ED?

In addition to its sedative hypnotic properties, propofol also has the potential to produce hypoventilation and apnea. Because of the monitoring practices used with procedural sedation, Class I prospective data are available concerning propofol's respiratory depression effects. The specific definition of hypoxia varied between studies, with some regarding pulse oximetry levels below 95% as hypoxia whereas others did not consider a patient hypoxic until saturations decreased below 90%.

If definitions of hypoxia or hypoventilation are accepted as study specific, then 7 studies with Class I to III evidence indicate that this occurs in 2% to 31% of patients sedated with a propofol bolus and infusion.^{37,66,70,72,78,79,82} In all but 1 of the studies, the hypoxia responded to minimal interventions such as head repositioning or supplemental oxygen. In 1 Class I study, oxygen desaturation occurred in 11.6% of patients, with no intervention required aside from supplemental oxygen.⁷² In another Class I study, the desaturation rate was

31% but was again transient, responding to jaw thrusts or supplemental oxygen.³⁷ In a single Class III study using high doses of propofol in an ICU setting, 20% of patients experienced hypoxia and 19% of patients required bag-valve-mask ventilation.⁸² This study was in marked contrast to data in all other studies, in which the highest incidence of bag-valve-mask ventilation was 2.5%. In the 2 studies evaluating propofol use for painless diagnostic sedation for MRI scans, the incidence of hypoxia was 5% to 10%.^{66,70}

Propofol also had hemodynamic effects associated with decreased peripheral vascular resistance when administered intravenously. Clinically insignificant transient decreases in blood pressure are reported in some patients, although in none of these patients was any intervention required.^{37,77,78,81,82}

Because of the hydrophobic nature of propofol, it must be delivered in a lipophylic suspension. Such vehicles can produce pain on injection of the drug. Clinical measures described to limit this effect include pretreatment of the vein with lidocaine and rapid infusion rates of normal saline solution with a slow injection of propofol.^{74,82}

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Propofol combined with opiate agents can be safely used for procedural sedation but may require head positioning, supplemental oxygen, and occasional bag-valve-mask ventilatory support.

Level C recommendations. Propofol alone, without the concomitant use of opiate agents, can be safely used for procedural sedation but may require head positioning, supplemental oxygen, and occasional bag-valve-mask ventilatory support.

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Evidentiary Table.

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Guldner et al ¹⁰	Retrospective pediatric rapid sequence intubation study in ED; intravenous dosing of etomidate with median dose 0.32±0.12 mg/kg; adjunctive medications included atropine in 78/105 (74%), lidocaine in 62/105 (59%), morphine in 3/105 (3%), and midazolam in 7/105 (7%); 105 charts; average age 3±2.9 y	The authors describe a slight increase in blood pressure; no episodes of myoclonus or seizure activity noted; there were no reported episodes of adrenal suppression determined either clinically or with laboratory testing as a result of etomidate administration	Design was retrospective; the main clinical endpoint was adrenal suppression	The authors note very little hemodynamic changes with the use of etomidate	Efficacy was not objectively measured	III
Sokolove et al ¹¹	Retrospective pediatric study evaluating rapid sequence intubation at 2 academic centers of both hospital and ED patients; etomidate IV dosing with mean dose of 0.37 mg/kg; adjunctive medications included lidocaine in 58/100 (58%), atropine in 37/100 (37%), and benzodiazepines in 9/100 (9%); 100 patients aged <10 y	Etomidate resulted in a mean blood pressure decrease of 1% during rapid sequence intubation; clinically important adrenal suppression was defined as the need for exogenous corticosteroid replacement for suspected adrenal insufficiency during the hospital course; inpatient records were available on 99 patients, and none of these patients received corticosteroids for suspected adrenal suppression	Design; only endpoints of study were hypotension and adrenal suppression; all patients were intubated	Based on a low incidence of hypotension and no important adrenal suppression	Efficacy was not objectively measured	III
Dickinson et al ¹²	Retrospective descriptive study in a university-based ED; 53 charts of children aged <18 y; all patients received IV etomidate (most received 0.1 to 0.2 mg/kg) and an IV opioid; a single etomidate dose was required in 40/53 (75%) patients and a second dose was necessary in 9/53 (17%) patients; 4/53 (7.5%) patients also received a dose of midazolam; 0.2-mg/kg initial bolus	There were no major adverse effects; 1 patient reported nausea, and another was given a fluid bolus for transient hypotension; no patient required ventilatory assistance; measure of efficacy was procedural success	Retrospective design; selection bias; documentation concerns as demonstrated by no reported cases of myoclonus	Results suggest that etomidate may be used safely in children, but the authors warn that further larger prospective studies are indicated	III	III
Ruth et al ¹³	2-phase feasibility study: retrospective pilot followed by a prospective descriptive study performed in a university-based ED; IV dosing in 9 patients in the pilot phase and in 51 patients in the prospective phase; a mean of 1.6 doses were required to complete procedures (range 1–3 doses); initial etomidate bolus used was 0.1 mg/kg; 18 patients included aged 1–25 y	Procedural success was achieved in 56/60 (93%) patients, with adequate sedation as documented by the physician in 59/60 (98%) patients; 12 complications were reported including oxygen desaturation below 90% (5), myoclonus (4), vomiting (1), pain with injection (1), and a "brief" bradycardic episode; none of the patients required ventilatory assistance	13 patients had missing nursing records, and another 4 patients lacked depth of sedation information	Etomidate administered IV for procedural sedation in the ED was both effective and safe in this group of patients	III	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Vinson and Bradbury ¹⁴	Retrospective observational study in 3 affiliated suburban EDs; chart review performed with prospective questionnaire sent to patients, with 120 (90%) completed; IV etomidate dosing with mean cumulative dose of 0.2 mg/kg; 134 total patients enrolled aged 6–93 y; 3 patients were aged 6–12 y and 12 patients included were aged 13–17 y	Moderate sedation was achieved in 48 (32%) patients, and deep sedation induced in 102 (68%) patients as measured by the Aldrete Postanesthetic Recovery Score; 5 (4.7%) of 7 adverse reactions were the result of oxygen desaturation requiring face mask oxygen; 4/5 also received bag-assisted ventilation; each of these patients were >55 y and had received relatively higher doses of etomidate, 0.23 mg/kg compared with 0.19 mg/kg in the nonrespiratory-compromised patients; no intubations; 2 patients experienced emesis; 114 (94%) responders stated they would be “extremely” willing to have this medication again	Design; few pediatrics; no standardized dosing; adjunctive medications given in 23% of procedures; only patients meeting ASA status I or II were candidates for procedural sedation; some patients were entered into the study more than once	The authors concluded that etomidate appears to be a brief, safe, and effective drug for emergency procedural sedation; however, the power of the study is not enough to evaluate incidence of all complications	III	III
Keim et al ¹⁵	Retrospective chart review in a university-based ED; the charts of 46 adults and 2 children, all receiving IV dosing were reviewed; mean initial dose of etomidate was 13 mg	10/48 (21%) of patients had adverse reactions; 1 (2%) patient had transient apnea requiring bag-valve-mask ventilation (this patient had multiple doses of analgesics as well); 1 (2%) patient required a nonrebreather for a desaturation <90%; emesis in 2 (4%) patients; anxiety in 2 (4%) patients; 4 (8%) patients had failed procedures	Design; limited pediatric patients; not an etomidate-only study, so some adverse side effects may be related to other sedatives and analgesics; documentation concerns as demonstrated by no reported cases of myoclonus	The authors conclude that although further study is indicated, etomidate holds promise as a procedural agent in the ED; the authors further stressed the need for adequate monitoring in the ED when using agents that may induce deep sedation	III	III
McDowell et al ¹⁶	Retrospective review of 971 pediatric oncology patients at a university hospital; 101 received IV etomidate (0.3 mg/kg) combined with either fentanyl or alfentanil for brief diagnostic or therapeutic procedures; all patients were <19 y	Etomidate was effective as defined by procedural success but was associated with more episodes of vomiting (9.9%) and agitation (4%) compared with propofol (0.5%) and (1.2%), respectively	Retrospective design; all 101 etomidate patients received narcotics for analgesia that could confound both the efficacy and safety data	Etomidate is an effective agent but had more vomiting and agitation when compared with propofol; however, propofol had a greater incidence of hypoxia (15.7%) than etomidate (2%)	Efficacy was not objectively measured	III
Schenarts et al ¹⁷	Prospective randomized controlled trial; included 10 etomidate and 8 control (midazolam) patients; each had a 4-h, 12-h, and 24-h cosyntropin stimulation test performed after standard drug administration during rapid sequence intubation induction in the ED; patients were ≥ 18 y, with a mean age of 58.4 y	Although a significant decrease in the normal adrenal response was noted at the 4-h level, all measured levels remained within normal levels throughout the study process; at 12 h, levels were no longer affected by the single 0.3-mg/kg induction dose	Study design does not evaluate clinical significance of brief adrenal suppression; no pre-induction cortisol levels were obtained; 13 additional patients were excluded	The authors concluded that, although a single dose of etomidate resulted in a decrease in normal adrenal response, adrenocortical levels remained in a normal laboratory range	Efficacy was not objectively measured	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Absalom et al ¹⁸	Prospective randomized trial; adrenocortical function of 35 critically ill patients was evaluated at pre-induction of general anesthesia in operating room with etomidate or thiopentone and after 24 h; each patient with an ASA status \geq III and aged \geq 16 y	The etomidate group was significant for more patients with an ACTH-stimulated cortisol increment $<$ 200 nmol/L; however, cortisol levels were never documented as low during the study	Number of patients aged 16–18 y not given; no baseline ACTH stimulation performed before induction; only 3 cortisol levels obtained; study power may be too small to show a significant difference	No significant difference between pre- and post-ACTH cortisol levels; significance of findings of the smaller ACTH-stimulated increment unclear	Efficacy was not objectively measured	III
Allolio et al ¹⁹	Prospective controlled trial; 29 patients undergoing general anesthesia induction were randomly assigned to etomidate or thiopentone, and ACTH and cortisol levels were measured up to 240 min after induction	The etomidate group had a significantly higher ACTH level and a significantly lower cortisol level; cortisol levels remained in a normal range	All patients were aged $>$ 14 y	The authors conclude that etomidate is safe for minor surgeries, but the adrenal suppression may cause problems for patients who require a greater adrenal response	Efficacy was not objectively measured	III
Allolio et al ²⁰	Prospective controlled trial evaluating the effect of a single induction dose of IV etomidate or thiopentone on adrenocortical function up to 210 min after induction; included 14 patients undergoing induction for general anesthesia; patient aged 14–74 y; with mean age for etomidate group of 45.5 ± 16.1 y	ACTH levels were elevated in the etomidate group but not to significant levels compared with the thiopentone group; demonstrated suppression of cortisol levels compared with thiopentone dosing	Time of day not noted	Authors found that despite inhibition of 11 β -hydroxylase after etomidate induction, no other comparable blockade of other enzymes in the corticosteroid-synthetic pathway could be demonstrated; confirmed previous data demonstrating suppression of cortisol levels with single etomidate dosing	Efficacy was not objectively measured	II
Helmert et al ²¹	Prospective double-blind controlled trial to determine if IV injection of droperidol or fentanyl before etomidate could attenuate side effects of pain and myoclonus; 83 patients aged 14–78 y with ASA status I, II, and III were enrolled; a severity score was assigned to pain and involuntary movements; operating room study	The incidence of pain on delivery in patients was: etomidate+normal saline solution 17% (5/29), etomidate+droperidol 16.7% (4/24), etomidate+fentanyl 18.5% (5/27); the incidence of myoclonus in patients was: etomidate+normal saline solution 37.9% (11/29), etomidate+droperidol 14.3% (3/24), etomidate+fentanyl 12.5% (3/24) ($P < .05$ for the groups using etomidate+another drug vs etomidate alone)	Not a sedation study; evaluated side effects during initial induction only; potential bias in scoring of pain and myoclonus	Both fentanyl and droperidol showed a significant difference in attenuating myoclonus after etomidate administration	Efficacy was not objectively measured	II

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Modica and Tempelhoff ²²	Prospective observational study; included 8 patients meeting ASA III–IV status with space occupying lesions and undergoing surgery; IV dosing; ages 18–71 y; anesthesia was induced with 0.2-mg/kg of etomidate followed by a 20-mg/min infusion	All patients monitored during induction with IV etomidate for EEG burst suppression and changes in intracranial pressure; the etomidate bolus required to reach burst suppression was 1.28 ± 0.11 mg/kg	No pediatric patients; small study size	Etomidate did result in significant reduction in intracranial pressure during intubation	Efficacy was not objectively measured	II
Pena and Krauss ²³	Prospective case series of 1,180 patients aged <21 y requiring procedural sedation in pediatric ED of large urban hospital using standard sedation record; midazolam and fentanyl used in 391, IV midazolam in 67, oral midazolam in 62, IN midazolam in 3; remainder used a variety of other drugs and combinations; 180 patients had IM ketamine/midazolam (3.30 ± 0.80 mg/unknown); 40 patients had IV ketamine/midazolam (1.31 ± 0.45 mg/unknown)	For fentanyl/midazolam: adverse event rate was 2.3%, with no serious or life-threatening complications; complications included oxygen desaturation in 10 (0.8%), paradoxical reaction in 7 (0.6%), emesis in 3 (0.25%), requirement for supplemental oxygen in 2 (0.17%); no significant differences between regimens; for ketamine/midazolam: 1.8% experienced adverse event (1 laryngospasm, 2 desaturations, 1 emesis)	Wide variety of agents and techniques; efficacy not measured; authors conclude that fentanyl/midazolam does not have increased rate of respiratory complications, but data show OR of 2.94 (95% CI 0.93–10.29, $P=.070$); small sample size for ketamine, selection bias, single center	Procedural sedation (fentanyl/midazolam or ketamine/midazolam) can be safely administered in pediatric ED by pediatric emergency physician; adverse event rate is low	Efficacy was not objectively measured	III
Sievers et al ²⁴	Prospective case series of 24 patients undergoing 70 pediatric oncology procedures using IV midazolam with (59%) or without (41%) morphine or fentanyl; mean age 7.83 ± 4.44 y (range 1.5–15.5 y); pediatric oncology clinic treatment room	Anxiety scores were highest on entry into treatment room and lowered during the procedure to levels approaching preprocedure baseline; restraint requirements were: much (20%), some (35%), none (45%); 13% experienced desaturation (oxygen saturation <90%), 14% required verbal stimulation, and 3% required oxygen; no patients required assisted ventilation or intubation; no serious complications; amnesia complete in 62%, partial in 28%	Sample size too small to make conclusions about adverse events; small sample size precludes conclusion that adding fentanyl to midazolam does not increase respiratory complications	Midazolam alone can cause respiratory depression in absence of narcotics; hypoxemia is dose related and subject to marked individual variation; observation period of 60 min after procedure appeared sufficient	III	III
Sandler et al ²⁵	Prospective, randomized crossover trial of midazolam vs fentanyl as premedication for painful oncology procedures; pediatric oncology clinic treatment room; mean age 10.04 ± 5.01 y (range 3.33–18.77 y); 86 procedures on 27 patients	No serious adverse events in either group; no episodes of oxygen desaturation <90%; efficacy (defined as patient/parent satisfaction) good in both groups; amnesia 91% for midazolam, 28% for fentanyl; patients/parents preferred midazolam 72% to 28%; OSBD scores increased from first procedure to last and decreased slightly for those choosing fentanyl	Small sample size; nonblinded assessment	Both agents are effective; patients and families prefer midazolam probably because of amnestic effects	II	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Hart et al ²⁶	Prospective, randomized, blinded experimental trial in 42 children requiring painful ED procedures treated with (1) fentanyl, (2) fentanyl-midazolam, or (3) MPC; all patients monitored for safety with ETCO_2 and pulse oximetry; efficacy was measured by objective clinical signs and subjective scale by blinded observers; mean age 4.8 ± 2.0 y (range 2–11 y)	Pain was measured by the 10-point scale of Broadman et al ⁸³ ; anxiety was measured using the author's 4-point scale; sedation was measured by the author's 5-point scale; author states that all scales were previously published and research assistants were trained in the use of scales; all equally efficacious; subclinical respiratory depression by hypoxemia or elevated ETCO_2 in 20% fentanyl, in 23% fentanyl-midazolam and in 11% MPC; prolonged sedation with MPC	The small sample size limits conclusions especially for safety concerns; the clinical relevance of documented transient hypercarbia in the absence of hypoxemia is not clear; the absence of any significant clinical events leaves the ETCO_2 data difficult to interpret	The new technique of noninvasive ETCO_2 monitoring may be a useful monitoring tool in the pediatric ED; fentanyl and midazolam cause a high incidence of subclinical respiratory depression	II	II
Kovooretal ²⁷	Prospective observational case series of 1,344 adults requiring 2–3-h electrophysiologic studies for cardiac arrhythmias; efficacy data are included on 775 patients and safety data on 1,344 patients; cardiac catheterization lab	No serious complications; insignificant changes in respiratory rate, oxygen saturation, ETCO_2 , and blood pressure; upper airway obstruction defined as snoring increases; increases in ETCO_2 or clinical evidence of upper airway obstruction occurred in 42%; restlessness occurred in 20%; 0.3% required conversion to general anesthesia for apnea or severe restlessness; efficacy in the sedation group was measured against those who had the study without sedation; in the sedated group vs the unsedated: no distress 74% vs 42%; moderate distress 24% vs 50%; extreme distress 2% vs 8%	All data are from adults; study was of continuous infusion of drugs rather than bolus for short procedure; procedure is 2–3-h electrophysiologic study primarily; this requires anxiolysis but not significant analgesia or sedation; applicability of these results to short painful procedures in children is questionable; no comparison group was used; observers of efficacy were not blinded	Continued infusion of fentanyl/midazolam can be safe and effective for adult electrophysiologic studies	III	III
Wright et al ²⁸	Retrospective case series of midazolam use in 389 patients in adult ED	Serious adverse event rate 1%; all serious adverse events associated with use of opiate drugs in addition to midazolam; efficacy defined as the procedure being accomplished and the physician not noting a problem	All adult patients; no standardized evaluation form	Midazolam is safe and effective when used in the ED in adult patients	Efficacy was not objectively measured	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Kennedy et al ²⁹	Prospective, single-blind, randomized, controlled trial of ketamine/midazolam vs fentanyl/midazolam in 260 patients, aged 5–15 y requiring orthopedic procedures in ED; ASA status I–II; videotaped blinded assessment of adequacy of sedation; safety assessed by objective monitoring; efficacy assessed by 9-point facial affective scale, parents 10-cm VAS, orthopedist satisfaction VAS, and OSBD-R scored by blinded observers and blinded treating physicians; midazolam ≤ 0.1 mg/kg, maximum 2.5 mg every 3 min until sedated; fentanyl ≤ 0.5 μ g/kg every 3 min until decrease response to verbal/painful stimuli vs ketamine ≤ 0.5 mg/kg every 3 min (up to 2 mg/kg) + glycopyrrolate 5 μ g/kg up to 250 μ g	Safety: hypoxia occurred in 6% of patients in the ketamine/midazolam group vs 25% of patients in the fentanyl/midazolam group, breathing cues needed 1% vs 12%, oxygen required 10% vs 20%; 2 patients in ketamine/midazolam group required assisted mask ventilation vs 0 in fentanyl/midazolam group; Efficacy: ketamine/midazolam had better efficacy measured by lower distress scores during procedure and increased orthopedic physician satisfaction; ketamine/midazolam had more vomiting in 2 wk after procedure (4% vs 0%); OSBD-R 1.08 ± 1.12 vs 2.70 ± 2.16 ($P \leq .0001$), parental pain VAS 4.21 ± 3.30 vs 5.55 ± 3.33 ($P = .004$), parental anxiety 4.48 ± 3.26 vs 5.49 ± 3.26 ($P = .02$), orthopedic satisfaction 8.71 ± 2.21 vs 9.61 ± 0.78 ($P = .0001$), equal induction time of 13 min, recovery time 113.7 ± 36.9 min vs 127.6 ± 56.2 min ($P = .02$), hypoxia 24% vs 6% ($P = .001$), breathing cues 12% vs 1% ($P = .001$), airway maneuver 11% vs 6% ($P = \text{NS}$), and bag-valve-mask 0% vs 2% ($P = \text{NS}$)	Study examined only orthopedic procedures; age range 5–15 y; results may not apply to younger patients; single-blind study	Well-done randomized controlled trial; ketamine/midazolam is more efficacious for sedation than fentanyl/midazolam for orthopedic procedures with less hypoxia and airway maneuvers; ketamine/midazolam is associated with fewer respiratory complications, but respiratory support may be needed with either regimen; vomiting in weeks following slightly more common with ketamine/midazolam (4% vs 0%)	I	I
Bauman et al ³⁰	Retrospective case series of randomly selected charts (convenience sample) (64/243) of sedation for lumbar puncture and BM biopsy in an outpatient oncology population; administered by pediatric critical care physician or anesthesiologist; nonstandardized treatments included multiple drug regimens; no data on fentanyl or midazolam use in absence of other agents; average age 6.6 y (range 3 mo to 15 y)	4/64 (6.25%) complications: 1/64 (1.6%) desaturation, 1/64 (1.6%) apnea, 1/64 (1.6%) hypotension, and 1/64 (1.6%) prolonged sedation; all complications were reversible and not serious; all procedures were completed; no complications with fentanyl/propofol	Very small study with small numbers in each group and much heterogeneity within each group; multiple agents used; difficult to glean efficacy or safety data about fentanyl and midazolam alone; retrospective descriptive study with no uniformity of data collection or observation of patients between groups	A fentanyl/propofol combination can be used in the pediatric population	Efficacy was not objectively measured	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
McQuillen and Steele ³¹	Prospective case series of 106 children undergoing ED sedation for painful procedures; patients assessed with ETCO ₂ monitoring; mean age 6.8 y (range 1.2–16.6 y)	Mean increase in ETCO ₂ during sedation was: for all sedation combined 6.7 (95% CI 5.8–7.5 mm Hg), for midazolam alone 3.2 (95% CI 2.2–4.2 mm Hg), for midazolam and ketamine 5.4 (95% CI 4.5–6.4 mm Hg), and for midazolam and opiate 8.8 (95% CI 7.4–10.2 mm Hg); percentage of patients with increased ETCO ₂ >10 mm Hg: for all sedation combined 19% (95% CI 0%–60%), for midazolam alone 9% (95% CI 3%–22%), for midazolam and ketamine 35% (95% CI 21%–50%), and for midazolam and opiate 50% (95% CI 13%–99%); all drug combinations used increased ETCO ₂ , but midazolam and fentanyl increased it to a greater degree than other agents	Did not measure efficacy; assessment not blinded; clinical significance of increased ETCO ₂ not clear	ETCO ₂ can be used as a monitoring adjunct in patients requiring sedation in the pediatric ED; midazolam/fentanyl causes more CO ₂ retention than other commonly used agents	Efficacy was not objectively measured	III
Graff et al ³²	Retrospective observational study of fentanyl and midazolam for 334 children undergoing orthopedic procedures (retrospective grading of depth of sedation); mean age 8.4±3.75 y; pediatric ED of large urban children's hospital	11% with some respiratory event (37 patients), with 2 patients requiring naloxone; 10% needed airway positioning or stimulation, but none required ventilation or intubation	Efficacy was not rigorously measured; this is the primary weakness of this study; retrospective study with no comparison group	Fentanyl and midazolam can be safely used for ED treatment of orthopedic injuries; close monitoring of respiratory status is essential	Efficacy was not objectively measured	II
Hostetler and Barnard ³³	Retrospective case series comparing ketamine/midazolam to fentanyl/midazolam in 93 children undergoing esophageal foreign body removal in the ED over a 2-y period; 57 (61.2%) of the 93 patients received ketamine/midazolam, 28 (30.1%) received fentanyl/midazolam, 5 (5.4%) received general anesthesia, and 3 (3.2%) received other; per protocol, midazolam was dosed initially at 0.05–0.1 mg/kg followed by 0.05-mg/kg subsequent doses; ketamine was given initially in 1–2-mg/kg IV doses followed by 0.5–1.0-mg/kg doses; fentanyl was given in 1–2-μg/kg IV doses initially, followed by 0.5–1.0-μg/kg; mean age 39.3±33.9 mo (range 3–168 mo)	Comparing ketamine/midazolam vs fentanyl/midazolam: mean procedure time 4.8 min (95% CI 3.7–6.0) vs 7.0 min (95% CI 5.1–8.9); mean length of stay 3.6 h (95% CI 3.3–3.9) vs 5.7 h (95% CI 3.0–8.3); transient hypoxia 10.7% (95% CI 6.6–14.8) vs 15.4% (95% CI 8.6–22.2); stridor 1.8% (95% CI 0–3.6) vs 0 (95% CI 0–1.9); and bag-valve-mask 3.6% (95% CI 1.1–6.1) vs 3.8% (95% CI 0.2–7.4)	Retrospective data collection and uncontrolled comparison; small sample size; removal of esophageal foreign body may cause hypoxia unrelated to sedation/analgesia	Ketamine/midazolam and fentanyl/midazolam are safe and effective for foreign body removal in children; recovery time appears longer for fentanyl/midazolam than for ketamine/midazolam	Efficacy was not objectively measured	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Bailey et al ³⁴	Randomized, blinded, prospective experimental trial of drug administration to 12 healthy adult volunteers to evaluate safety profile	Midazolam alone produced no significant respiratory effects; fentanyl alone produced hypoxemia in 50% of subjects, hypoxemic episodes were defined as SpO ₂ <90% and lasting ≥ 10 s; decreased ventilatory response to CO ₂ , and apnea in 0%; combination of fentanyl and midazolam produced hypoxemia in 92%, decreased ventilatory response to CO ₂ similar to but no worse than fentanyl, and apnea in 50%	Small sample size for safety study limits conclusions; study done in adults; it is not clear how dosage, adverse effect profile, and responses to decreased ventilatory response to CO ₂ will affect children in the clinical setting; study of drug effect in healthy volunteers with no painful stimulus may be difficult to translate to children undergoing painful procedures	Combination of fentanyl and midazolam markedly increase risk of hypoxia and apnea in comparison to either agent alone	Efficacy was not objectively measured	III
Milgrom et al ³⁵	Randomized, blinded, placebo-controlled trial of midazolam, fentanyl, and methohexital in various combinations in 207 adults undergoing dental procedure (molar extraction); university dental clinic	Midazolam fentanyl combination resulted in greater efficacy but increased level of sedation and complications; efficacy measures included observer-reported sedation score and self-reported pain and anxiety scores; apnea in 63% of midazolam and fentanyl and in 3% midazolam alone	All adult data but well-done study of drug use in painful procedures	High rate of apnea in combination group does not justify its use based on small increase in sedation effect	II	II
Yaster et al ³⁶	Case report	Respiratory arrest in a 13-month-old toddler receiving midazolam and fentanyl	Anecdotal	Midazolam and fentanyl are respiratory depressants	X	X
Godambe et al ³⁷	Prospective, partially blinded, randomized (videotaped) controlled trial in convenience sample of patients; ASA status I–III for orthopedic procedures in ED; 59 patients given IV propofol (1 mg/kg initially with smaller aliquots)/fentanyl (1–2-μg/kg aliquots) vs 54 patients given ketamine (1–2-mg/kg)/midazolam (0.05 mg/kg aliquots); measurement of sedation and recovery times; use of OSBD-R and Likert satisfaction scores for orthopedist and nurse, and VAS for parents; 113 patients aged 3.1–16.3 y (median 9.0 y)	Total sedation and recovery time for propofol/fentanyl vs ketamine/midazolam 38.9 min vs 62.1 min ($P<.0001$) and 54.2 min vs 20.8 min ($P<.0001$), respectively; transient desaturation (responsive to jaw thrust or head repositioning or supplemental oxygen) occurred in 18/59 (31%) of propofol/fentanyl patients vs 4/54 (7%) of ketamine/midazolam patients ($P=.002$); mean OSBD-R during manipulation for propofol/fentanyl vs ketamine/midazolam 0.278 on scale of 0–23.5, with 0 representing no distress, vs 0.084 ($P=.787$); for propofol/fentanyl vs ketamine/midazolam: orthopedic satisfaction 4.85 vs 4.93 ($P=.245$), nurse satisfaction 4.85 vs 4.95 ($P=.173$), and parental VAS 8.7 vs 13.0 ($P=.380$)	No significant limitations; partially blinded only; loss of videotaping in 3 patients	Both propofol and ketamine are safe and effective for ED orthopedic procedures; propofol/fentanyl had significantly shorter sedation times and longer recover times than ketamine/midazolam and equivalent satisfaction scores; there were significantly more transient desaturations with propofol/fentanyl than with ketamine/midazolam	I	I

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Acworth et al ³⁸	Single-blinded (sedation assessment), randomized, controlled trial; ketamine 1 mg/kg/midazolam 0.1 mg/kg IV vs IN midazolam 0.4 mg/kg; laceration repair and foreign body removal; VAS (author's sedation scoring system); age 6 mo to 12 y; ED study; total of 53 patients	"Adequate" sedation in 27/27 vs 24/26 ($P=NS$), onset 2.0 min vs 7.3 min ($P<.001$), time to discharge 97.9 min vs 79.0 min ($P=.02$), average sedation score at 30 min: 2.4 vs 3.5 ($\Delta 1.1$, 95% CI 0.7–1.4, $P<.001$), average VAS (author's scoring system used) at 30 min: 1.8 vs 3.8 ($\Delta 2.0$, 95% CI 1.1–2.9, $P<.001$), overall VAS 2.1 vs 4.5 ($\Delta 2.4$, 95% CI 1.1–3.6, $P=.001$); physician satisfaction "excellent/good" 88% vs 54%, $P=.006$, parental satisfaction "excellent/good": 92% vs 65%, $P=.02$; one significant adverse event: saturation <90% in the ketamine group	Treating physician and nurse not blinded; small study for adverse events	IV ketamine/midazolam superior to IN midazolam in sedation onset, time to discharge, sedation scores, and physician and parental satisfaction	II	II
Petrack et al ³⁹	Double-blinded randomized, controlled trial 12 h/d with research assistant; patients aged 6 mo to 6 y requiring sedation for wound repair, burn care, or lumbar puncture; randomized to ketamine 4 mg/kg/atropine 0.01 mg/kg IM vs meperidine 2 mg/kg/promethazine 1 mg/kg/chlorpromazine 1 mg/kg IM; ED study; total of 27 patients	15 patients received ketamine vs 12 received MPC; ages 31 ± 20 mo vs 39 ± 22 mo, onset of sedation 3 min vs 18 min ($P<.01$), duration 82 min vs 97 min ($P=.15$), time to discharge 85 min vs 113 min ($P=.01$), and mean OSBD-R score 2.7 (95% CI 0.4–4.9) vs 9.8 (95% CI 4.9–14.6, $P<.003$); there were no significant adverse effects seen in either group	Small numbers for adverse effects; patients only recruited 12 h/d	Ketamine is superior to MPC in time of onset of sedation, time to discharge, and mean OSBD-R score; the durations of sedation were similar	I	X
McGlone et al ⁴⁰	Prospective nonrandomized comparison of IM ketamine 2.5 mg/kg + atropine (additional 1 mg/kg given prn) versus IN midazolam 0.5 mg/kg for laceration repair age 12 mo to 7 y; used nonvalidated, simple 4-point behavior scales; ED study; 102 patients, average age 3.6 y	For ketamine vs midazolam: during anesthetic injection 96% vs 38% and during suturing 100% vs 70% patients were cooperative/intermittent crying ($P<.01$); 18% vs 8% had vomiting ($P=.234$), median SpO_2 97% for both, recovery behavior quiet or mild agitation in 92% vs 86% ($P=.44$)	Nonblinded alternating of sedative	IM ketamine 2.5 mg/kg more effective than IN midazolam for suturing	III	II
Dachs and Innes ⁴¹	Prospective nonrandomized study; patients aged 18 mo to 8 y; brief painful procedures; IV ketamine 1–1.5 mg/kg \pm atropine; ED study; 30 patients	Median age 38 mo, 90% laceration repair, local anesthesia used in 52%; 1mg/kg dose resulted in 6/11 (54%) patients requiring additional ketamine, dose increased to 1.5 mg/kg during study, 1.5 mg/kg dose resulted in 1/18 (5.5%) patients requiring additional ketamine; all patients were unresponsive to painful stimulation (endpoint); SpO_2 >93% on room air for all patients; telephone follow-up in 96.6%: 1 patient vomited in recovery, 1 at home, 9 with ataxia for 0.5–2 h and no nightmares	Small sample size, nonblinded outcome assessments	IV ketamine at 1.5 mg/kg effective for procedural sedation	III	II

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
McCarty et al ⁴²	Prospective cohort of patients aged 12 mo to 11 y undergoing orthopedic procedures using ketamine by standard protocol; emergency physician monitored sedation along with nurse while orthopedist did reduction and measured sedation with CHEOPS; 99 received 2 mg/kg IV ketamine and 15 received 4 mg/kg IM ketamine; ED study; total 114 patients	Average onset to reduction for IV: 96 s (20 s to 5 min) and IM: 4 min 42 s (60 s to 15 min); average CHEOPS score 6.4 (5–10) and all had adequate sedation for reduction; emesis in 8 (7%), nausea in 5 (4%), ataxia in 8 (7%), and dysphoria in 1 (1%); time to discharge IV: 84 min (22–215 min), IM: 90 min (60–130 min)	Nonrandomized study; small numbers for serious adverse effects	IV and IM ketamine allowed adequate sedation for fracture and/or joint reduction without serious adverse effects; IV ketamine has a rapid onset of action, both IV and IM ketamine have a fairly prolonged recovery time	II	II
Pruitt et al ⁴³	Prospective, single-arm trial of IM ketamine 3 mg/kg/ midazolam 0.05 mg/kg/ glycopyrrolate for lacerations/dental procedures in patients aged 1–7 y; additional ketamine 1 mg/kg prn; nonvalidated, simple behavior scales during procedure and recovery (SpO ₂ , etc); ED study; 42 patients (average age 2.7 y)	Onset average 4.8 min (3–10 min); recovery average 76 min (50–120 min); 26/37 patients cooperative/ sleeping; 11/37 patients intermittently crying/ fighting, 5/11 got additional 1 mg/kg of ketamine; heart rate increased 18%, respiratory rate increased 13%, SpO ₂ >96% in all; no airway adverse events; emesis in 2 patients	Nonrandomized trial; small number of patients to assess frequency of major adverse events	IM ketamine/ midazolam/ glycopyrrolate safe and effective	III	II
Wathen et al ⁴⁴	Double-blind randomized, controlled trial of patients aged 4.5 mo to 16 y requiring sedation, ASA status I–II; received ketamine 1 mg/kg/ glycopyrrolate 5 µg/kg IV ± midazolam 0.1 mg/kg IV; videotaped blinded assessment using OSBD-R; ED study; 266 patients	129 had ketamine alone, 92% fracture reduction or wound repair; total sedation time: 78 min (60–100 min) vs 75 min (60–95 min), Δ3 (95% CI –5 to 10), recovery agitation 7.1% vs 6.2%, Δ0.8 (95% CI –5.3 to 7.0); desaturations 1.6% vs 7.3%, Δ –5.7% (95% CI –5.7% to –0.9%); emesis: 19.4% vs 9.6%, Δ9.8% (95% CI 1.4%–18.2%); for patients >10 y: recovery agitation 5.7% vs 35.7%, Δ–30.0% (95% CI –49.3% to –10.7%)	None	Adding midazolam to ketamine does not increase sedation time, does not decrease recovery agitation; increases recovery agitation in patients >10 y, but decreases emesis	I	I
Kim et al ⁴⁵	Pilot study of sidestream ETCO ₂ monitoring for consecutive patients aged 12 mo to 15 y ASA status I–II receiving IV ketamine (1.5 mg/kg)/atropine 0.01 mg/kg, minimum 0.1 mg, maximum 0.5 mg for procedural sedation; ED study; total of 27 patients	20 of 27 patients in whom ETCO ₂ monitoring was attempted had usable data; no significant change in ETCO ₂ and SpO ₂ ; no ETCO ₂ >47 mm	Selected small pilot study	Ketamine appears to not induce hypoventilation	Efficacy was not objectively measured	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Sherwin et al ⁴⁶	Double-blind randomized, controlled trial; patients aged 12 mo to 15 y undergoing short, painful procedure in ED; ketamine 1.5 mg/kg/atropine 0.01 mg/kg IV ± midazolam 0.05 mg/kg up to 2 mg; 0–100 mm VAS (author's scoring system used) for agitation; 104 patients	53 patients received midazolam; recovery agitation VAS (author's scoring system used) 4 mm (IQR 2–19 mm) vs 5 mm (IQR 3–14 mm), $P=.70$; adequate sedation 100% vs 100%, $P=1.00$; recovery 61 min (40–98 min) vs 64 min (44–79 min) $P=.57$; airway complication 4% vs 2%, $P=1.00$; emesis 2% vs 12% ($\Delta=10\%$, 95% CI –20% to 0%, $P=.058$)	None	Midazolam does not decrease recovery agitation when ketamine is used for sedation; there is a strong trend to less emesis	I	II
Holloway et al ⁴⁷	Retrospective chart review of all children who received ketamine over a 20-mo period, primarily for laceration repair; no standardized sedation record; follow-up parent standardized interview regarding: adverse effects, mean 5 mo (range 1 wk to 14 mo) postsedation; ED study; 100 patients	78% of patients had wound repair, all IM, mean dose 5.5 mg/kg (range 3.65–8.91 mg/kg); no admissions or "airway problems" noted; vomiting during recovery in 14%, after discharge in 12%; agitation/nightmares in 2%, "unusual behavior" in 4%	Retrospective review; no standardized sedation records	Ketamine is safe when administered IM for short painful procedures	Efficacy was not objectively measured	III
Hostetler and David ⁴⁸	Prospective cohort of patients aged 6 mo to 18 y; received ketamine 0.5 to 1.5 mg/kg/midazolam 0.035 to 0.05 mg/kg/atropine 0.01 mg/kg IV and prehypnotic suggestion; sedative redosing with ketamine 0.5–1.0 mg/kg IV; 1 physician and nurse monitored sedation, and second physician did procedure; ED study; 301 eligible patients recruited	68.8% of patients for orthopedic procedures, 20.6% for wound care, and 10.6% other; 205 patients aged <10 y, 96 aged ≥ 10 y; physician and nurse evaluation of behavioral reaction $\kappa=0.77$; for patients aged <10 y: 7/205, 3.4% (95% CI 0.9%–5.9%) had mild reaction, 2/205, 1.0% (95% CI 0%–2.4%) had severe reaction; for patients aged ≥ 10 y: 2/96, 2.1% (95% CI 0%–5.0%) had mild reaction, 4/96, 4.2% (95% CI 0%–8.2%) had severe reaction; 13.2% of 167 patients followed up had nighttime awakening; overall 97.5% of parents were satisfied, 98.1% for patients not having behavioral reaction, 80.0% for patients suffering behavioral reaction	Behavioral reaction measurement not validated; not randomized or blinded; phone follow-up for approximately 50% of the patients	There is a low rate of mild or severe behavioral reaction to ketamine with a moderate number suffering nighttime awakening; there is good parental satisfaction with ketamine sedation	Efficacy was not objectively measured	II

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Green et al ⁴⁹	Retrospective cohort study of children aged <15 y receiving IM ketamine in 2 EDs following a treatment protocol; used multiple logistic regression to test predictor variables (ie, age, sex, ASA status, quantity of first ketamine dose, number of doses) for adverse events; protocol dictated initial IM dose of 4 mg/kg with repeat allowed in 5–10 min of another IM dose of 2–4 mg/kg; 1,022 patients	No association of risk factors for airway complications; emesis increased with age: OR 1.25/y (95% CI 1.17–1.34, <i>P</i> <.001); recovery agitation associated with ASA status >I: OR 3.05 (95% CI 1.65–7.30, <i>P</i> =.004) and decreasing age: OR 0.79 (95% CI 0.69–0.89, <i>P</i> <.001)	Retrospective data collection	Recovery agitation associated with higher ASA status but decreasing age; emesis is associated with increasing age; effects are not large and may not be clinically important	Efficacy was not objectively measured	II
Green et al ⁵⁰	9-y retrospective cohort study of children aged <15 y receiving IM ketamine in 2 EDs following a treatment protocol; some prospective data collection for sedation (42% of cases), supplemented by chart review; unvalidated outcome measures; protocol dictated initial IM dose of 4 mg/kg with repeat allowed in 5–10 min of another IM dose of 2–4 mg/kg; 1,022 patients	4.4% of the patients were ASA status >II, 86.5% for wound and orthopedic procedures, 4% were critical care procedures; “adequate” sedation in 98%, 215 patients required >1 dose; adverse events included airway complications in 1.4% without intubation or sequelae, emesis without evidence of aspiration in 6.7%, mild recovery agitation in 17.6%, moderate-to-severe agitation in 1.6%, and no hospitalizations due to ketamine; median time from ketamine administration of a single dose to discharge was 110 min	Retrospective series, <50% compliance with data collection form; nonblinded and unvalidated outcome measures	Ketamine in this very large cohort has a low rate of significant adverse events without serious sequelae	Efficacy was not objectively measured	II
Green et al ⁵¹	9-y retrospective cohort study of all children aged <15 y who received IV ketamine for procedural sedation using treatment protocol at 2 centers; initial dose 1.5±0.5 mg/kg, total dose 2.5±1.6 mg/kg, 31% received midazolam; ED study; 156 patients, average age 6.3±3.2 y	81% of patients for orthopedic or wound management, 6% for endotracheal intubation and 13% miscellaneous, 17 with ASA status III–IV; adverse events: 1 with apnea with rapid IV infusion, 1 with respiratory depression requiring jaw thrust only, and 6 with emesis without evidence of aspiration; median recovery time 103 min (IQR 76–146 min)	Mixed indications for use of IV ketamine; retrospective data collection; not blinded	IV ketamine appears safe even in high-risk patients	Efficacy was not objectively measured	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Green et al ⁵²	Prospective uncontrolled cohort, age 14 mo to 13 y requiring sedation for painful procedures; protocol: IM ketamine 4 mg/kg; unvalidated sedation assessment; ED study; 108 patients, mean age 54 mo	75% of patients with lacerations, 9.3% orthopedic procedures; 86% procedures completed without local anesthesia, 7% received local, 3% needed additional ketamine; onset by 5 min in 83%, recovery mean 82±33 min, recovery behavior quiet in 80%, mild agitation in 17%, moderate agitation in 3%, pronounced agitation in 1%, laryngospasm in 1 after study completed, and emesis in 6	Uncontrolled unvalidated trial; unblinded outcome measures; small sample size for safety	Ketamine is effective for brief painful procedures with a low rate of adverse effects	III	II
Green et al ⁵³	Retrospective 5-y cohort of non-ED patients, ages <1 mo to 21 y, receiving IV ketamine/midazolam to facilitate gastrointestinal procedures (86% esophagoscopy); median ketamine dose 1.3 mg/kg, 46% patients ASA status ≥ III	636 patients given ketamine, 86% for esophagoscopy; laryngospasms noted in 8.2% overall, and in 14% of preschoolers; median lowest oxygen saturation, if recorded, with laryngospasms was 70% (range 30%–89%); 37% received positive pressure ventilation	Retrospective design with no comparison group; the main clinical efficacy endpoint was accomplishment of procedure; safety endpoints were adverse cardiopulmonary events that were not routinely recorded (eg, lowest oxygen saturation, presence/absence of laryngospasm)	Authors conclude no adverse outcomes attributable to ketamine	Efficacy was not objectively measured	X
Forbes et al ⁵⁴	Prospective observational study to examine hemodynamic effects of rectal methohexital (25 mg/kg) through echocardiography in operating room; the study included 12 patients aged 32.4±3.8 mo	Methohexital had increased heart rate but had no effect on other parameters; no arterial desaturation or apnea	Study did not effectively examine apnea or desaturation but only echocardiographic effects	Rectal methohexital has minimal hemodynamic effects	Efficacy was not objectively measured	III
Manuli and Davies ⁵⁵	Retrospective study of CT and MRI patients; non-ED study; 25 mg/kg of methohexital given rectally; 94 patients aged 25±2 mo	Sleep was induced in 81% of children; 1% desaturation rate	Retrospective nature and methods prevented valid conclusions on efficacy; deduced from chart	Rectal methohexital is safe	Efficacy was not objectively measured	II
Pomeranz et al ⁵⁶	Prospective observational study of ED patients undergoing CT scan; 25 mg/kg of methohexital given rectally; efficacy was determined with 2 separate measures: a 3-point scale recorded the need for restraints to complete the CT study while another scale recorded the quality of the CT scan as determined by the presence of motion artifact; 100 patients with average age of 24 mo	95% efficacy; 3% required bag-valve-mask ventilatory support briefly, no endotracheal intubations, 2 head repositionings, and 2 given nasal oxygen	None; complications may not be as severe as noted because bag-valve-mask ventilatory support was by protocol	Methohexital safe and effective for CT scanning	I	I

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Sedik ⁵⁷	Retrospective and prospective observational study; IV methohexital in ED patients for CT scans; used a dosing range of 0.5–2 mg/kg; efficacy was determined by the ability to complete the CT scan; 55 patients; 2-phase study—phase 1 patient age: 28±24 mo; phase 2 patient age: 27±17 mo	1% of patients had oxygen saturation <93%, and 1% had a failure rate of sedation	Part of the study was done retrospectively, although the prospective portion compensates	Methohexital is safe and effective with brief duration of action	II	II
Varner et al ⁵⁸	Prospective observational study of 10 mg/kg IM methohexital for CT studies; 2 different strengths examined (3.5% and 5%); efficacy was determined by the ability to complete the CT scan; non-ED study with 50 patients aged 2 mo to 5 y	Efficacy data only, 92% effective for CT	Safety data are not well documented, although no apnea was noted	Methohexital is effective at 10 mg/kg	II	Safety was not objectively measured
Schwanda et al ⁵⁹	Retrospective observational study of hematology/oncology patients; 1 mg/kg IV methohexital; efficacy was determined by the ability to complete hematology/oncology procedure; because the drug was titrated by the physician to the endpoint of cooperation with the procedure, the drug was 100% effective; 132 procedures in 33 patients aged 8.3±5 y	100% effective; 1.5% needed bag-valve-mask ventilatory support, 17% had decreased blood pressure, 5.3% had complications with intervention	Safety data were prospectively collected and are grade II; the efficacy data were collected through chart review and should be regarded as grade III; not truly reflective of ED patients; the use for lumbar punctures may be of some value	Slightly higher complication rate than reported in other studies	III	II
Rooks et al ⁶⁰	Prospective, nonblinded study; 317 children in pentobarbital group; 358 children in chloral hydrate group; total of 675 patients; comparison of oral pentobarbital to oral chloral hydrate; pentobarbital at dose of 4 mg/kg/dose; chloral hydrate at dose of 50 mg/kg/dose; radiology study; patients in the oral pentobarbital group were sedated for MRI (230 patients), CT (85 patients), nuclear medicine (1 patient), and interventional radiology (1 patient) procedures. In the chloral hydrate group the breakdown was as follows: MRI (268 patients), CT (87 patients), nuclear medicine (1 patient), and interventional radiology (2 patients) procedures	Oral pentobarbital: time to sedation 19±14 min; time to discharge 100±35 min; length of sedation 81±34 min; adverse reactions 1.6%; sedation was unsuccessful in 1 patient (0.3%) in the oral pentobarbital group; Oral chloral hydrate: time to sedation 16±11 min; time to discharge 103±36 min; length of sedation 81±34 min; adverse reactions 1.7%; sedation was unsuccessful in 1 patient (0.3%) in the chloral hydrate group	Radiology study, fasted patients	Similar time to sedation, time to discharge, length of sedation, and adverse reactions	II	II

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Greenberg et al ⁶¹	Prospective, nonblinded study included 100 children; pentobarbital dose 6 mg/kg in 3 divided doses to a maximum of 200 mg; age range 2–15 y with a mean age of 6.8 y; radiology department study; all patients had MRI	8% (8 children out of 100) that failed were either ≥ 12 y or weight was >50 kg; side effects: 7% hyperactivity, 6% oxygen desaturation, 3% cough, 2% prolonged sedation, 1% vomiting	Routine and fasted studies	The success rate was good, it could be improved if the use was limited to children <12 y and weighing <50 kg	II	II
Karian et al ⁶²	Retrospective study included 1,665 children; children aged <1 y were sedated with chloral hydrate (50–100 mg/kg) or oral pentobarbital (4–8 mg/kg); children aged >1 y received IV sedation, pentobarbital IV 2–6 mg/kg, fentanyl 1–2 μ g/kg if required; midazolam dose of 0.05 mg/kg IV or 0.5–0.75 mg/kg orally; 216 patients were >10 y; radiology study—1,665 pediatric patients had sedation for various radiology studies, of these 1,110 had a scan (302 MRI, 179 CT), 675 patients received IV contrast	Paradoxical reaction in 1.2% and decreased oxygen saturation in 0.5% of patients who recovered with head positioning; sedation failure rate of 1%	Radiology study; fasted patients; multiple drug regimens	Pentobarbital has a low sedation failure and few adverse reactions	III	II
Mason et al ⁶³	Prospective, nonblinded; study included 1,070 children; pentobarbital compared with combination of pentobarbital and midazolam; pentobarbital group received 2–6 mg/kg IV; pentobarbital-midazolam group received an initial 0.1 mg/kg of IV midazolam followed after 1 min by 2–6 mg/kg IV pentobarbital; in both groups, all pentobarbital was titrated to effect in standardized 1–2 mg/kg doses; age in pentobarbital group: 3.3 ± 2.5 y; age in pentobarbital/midazolam group: 4.3 ± 2.7 y; radiology study; pentobarbital group: MRI 482 (75%), CT 120 (19%), nuclear medicine 22 (3%), and MRI combined with CT 16 (3%); pentobarbital-midazolam group: MRI 340 (79%), CT 65 (15%), nuclear medicine 20 (5%), MRI combined with CT 5 (1%)	The success rate of the pentobarbital alone group was 99.5% vs 99.8% in the pentobarbital-midazolam group; the use of midazolam increased time to sedation (pentobarbital-midazolam 8.0 ± 4.4 min vs pentobarbital 6.5 ± 4.4 min) and also prolonged the time to discharge by approximately 14 min when used in conjunction with pentobarbital (pentobarbital-midazolam 120 ± 32 min vs pentobarbital 106 ± 34 min)	Radiology study; fasted patients	No beneficial effect by adding midazolam to pentobarbital; it actually increased the time to sedation and the time to discharge	II	I

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Strain et al ⁶⁴	Prospective, nonrandomized, nonblinded, no comparison group; study included 225 children; 2–6 mg/kg were given in the following manner: 2.5 mg/kg IV and patient is observed for disconjugate eye movement, yawning, quiet sleep, or a slowed respiratory rate, wait 30 s then if still active give 1.25 mg/kg, wait 30 s, then the remaining dose of 1.25 mg/kg was given if the patient did not become quiet over the next 30–60 s; occasionally an additional dose of 1 mg/kg was given to a total dose of 6 mg/kg; the patients received a mean dose of 4.5 mg/kg; 25% of patients aged 6 wk to 6 mo; 30% of patients aged 6 mo to 1 y; 30% of patients aged 1–3 y; upper age limit not given; radiology study—sedation for CT imaging	7.5% transient desaturation to $\leq 80\%$: oxygen normalized spontaneously in 14 patients (sample size 225) and 2 patients needed head positioning; sedation failure rate $< 1\%$	Radiology study; fasted patients	IV nembutal is safe, effective, and efficient form of sedation for pediatric CT imaging	II	II
Moro-Sutherland et al ⁶⁵	Prospective, randomized, nonblinded; study included 55 children aged 6 mo to 6 y; compared pentobarbital vs midazolam; standardized dose of midazolam: total dose 0.2 mg/kg (maximum dose 7.5 mg); pentobarbital: total dose of 5 mg/kg (maximum dose 100 mg); protocol for the administration of midazolam: IV midazolam 0.2 mg/kg drawn up, 0.1 mg/kg IV over 2 min, wait 2 min, 0.05 mg/kg IV over 2 min, 0.05 mg/kg IV over 2 min; dose titrated against response; protocol for the administration of pentobarbital: IV pentobarbital 5 mg/kg drawn up, 2.5 mg/kg IV over 30 s, wait 1 min, 1.25 mg/kg IV over 30 s, wait 1 min, 1.25 mg/kg IV over 30 s, dose titrated against response, average dose was 3.75 mg/kg; radiology study—sedation for head CT	With pentobarbital, 97% of patients scanned successfully; induction time 6 min, duration of sedation 86 min; with midazolam, 19% of patients scanned successfully; mild oxygen desaturation, oxygen saturation $> 90\%$	Radiology study; fasted patients; only 55 patients; not blinded to outcomes	IV pentobarbital is more effective than IV midazolam for sedation of children requiring CT imaging	II	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Kain et al ⁶⁶	Prospective, randomized, nonblinded controlled trial comparing propofol with a combination of thiopental and pentobarbital for MRI studies in radiology suite; study included 58 patients; 29 patients received 1–2 mg/kg of propofol followed by propofol infusion 5.4 mg/kg/h, and second group received 1–3 mg/kg of thiopental followed by a pentobarbital bolus of 2–3 mg/kg, and supplemental doses of 1–2 mg/kg of thiopental; ages 11 mo to 6.5 y; radiology study—MRI of the brain or spine	Time to recovery in propofol group was 19±7 min vs 35±20 min in thiopental/pentobarbital group; time to discharge in propofol group was 24±6 min vs 40±11 min in thiopental/pentobarbital group; for propofol group: 5% pulse oximetry level desaturation <90% and 4% for thiopental/pentobarbital group with all events responding spontaneously or to head repositioning; all studies were completed, and the average MRI quality score was comparable in both groups	Radiology study; fasted patients; sample size is a minor limitation	Propofol and pentobarbital are safe for use in painless diagnostic studies; propofol and pentobarbital had similar desaturation levels; pentobarbital had longer recovery time and longer time to discharge than propofol	II	III
Egelhoff et al ⁶⁷	Retrospective, observational study; study included 6,006 children; oral chloral hydrate was given to infants aged <18 mo, the initial dose was usually 50–75 mg/kg with additional doses of 25–50 mg/kg up to 100 mg/kg as needed; nebutal (3–8 mg/kg) was started at 3 mg/kg in children >18 mo; fentanyl was added if painful procedure at a dose of 1 µg/kg up to 3 µg/kg; patient ages: 1 d to 18 y; radiology study; imaging studies included CT, sonography, MRI, special procedures, and nuclear medicine (actual number of patients included in each group was not specified)	Sedation failure rate was 1%; 0.06% required overnight hospitalization; transient respiratory depression to oxygen saturation <10% below the baseline despite repositioning; vomiting in <0.53% of patients; irritability in 0.21% of patients	Radiology study; fasted patients; 3 different drug regimens were used: chloral hydrate, pentobarbital, and pentobarbital with fentanyl	This study looked mainly at the use of chloral hydrate and pentobarbital alone or pentobarbital in combination with fentanyl; however, additional drugs were used including but not limited to diazepam and midazolam; the sedation failure rate was 1% and the rate of complications was low	III	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Slovic et al ⁶⁸	Prospective study; study included 549 children, above or below 8 y; 70% <8 y, of those 48% were <4 y; multiple drug regimens: chloral hydrate, pentobarbital, midazolam, diazepam, and with any of these drugs fentanyl was used for enhancement; dosing: oral chloral hydrate either 50 mg/kg or 75 mg/kg given depending on weight, age, and length of examination, up to a maximum of 1,000 mg, age <12 mo, optional use at age 12–18 mo; IV pentobarbital 3 mg/kg for ≥12 mo, 1 μg/kg fentanyl given if not asleep 5 min after pentobarbital; IV fentanyl 1 μg/kg at any age, used mostly for pain; IV midazolam 0.2–0.3 mg/kg × 2, with 2–5 min between doses, use for children aged ≥8 y; oral diazepam 5–10 mg in children aged >5 years, used on anxious older children in MRI; radiology study; imaging procedures included MRI (1,202 patients), CT (1,238 patients), nuclear medicine (162 patients), ultrasound (9 patients), diagnostic imaging (6 patients), and special procedures (240 patients)	With pentobarbital 8.4% hyperactivity in children >8 y and 19% sleeping for >8 h; if multiple doses of pentobarbital were used, there was a significant short-term effect on children <8 y, with 35% sleeping >8 h after the MRI; among 2,857 patients sedated in a 12-mo period, there were 40 failures (1.4%), complications (all minor) in 142 (5%); among the 2,857 patients, 1,202 had an MRI, with 26 failures (2.2%) including hyperactivity and vomiting, and 1,238 had a CT	Radiology study; fasted patients	Hyperactivity was found only in those children who received pentobarbital; the association of pentobarbital with hyperactivity was statistically significant for all ages when compared with drug regimens not containing pentobarbital	II	II
Sanderson ⁶⁹	Retrospective study; study included 149 children aged 3 mo to 7 y and 3 mo; children undergoing abdominal CT scan with oral contrast media, therefore not NPO; 141 patients received pentobarbital as the only sedative agent (94.6%), 8 patients (5.4%) required supplemental sedation with midazolam, with 1 patient requiring both midazolam and fentanyl; pentobarbital average dose 4.6 mg/kg; midazolam average dose 0.18 mg/kg (range 0.13–0.27); fentanyl was given to 1 patient at a dose of 2 μg/kg; radiology department	Abdominal CT with oral contrast was completed in all patients; 14% complication rate: desaturation, vomiting, airway secretions, airway obstruction, coughing, and bronchospasm	Retrospective study; radiology department; abdominal CT, however, patients were not NPO and had received oral contrast 45 min before the scan	Pentobarbital was an effective sedation agent with abdominal CT scan completed in all patients; complication rate was high (14.7%); some of the complications included desaturation, vomiting, and cough	III	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Bloomfield et al ⁷⁰	Prospective, randomized, controlled, nonblinded trial; pentobarbital compared with propofol; dosing: pentobarbital IV in successive boluses of 2.5 mg/kg to a maximum of 7.5 mg/kg; propofol IV 2 mg/kg (with supplemental 1-mg/kg boluses) followed by continuous infusion of 6–10 mg/kg/h; efficacy was determined by the ability to complete MRI study; MRI patients, radiology study; pentobarbital group mean age 4 y; propofol group mean age 5 y; age range 2–11 y; 61 total patients, 31 propofol cases and 30 pentobarbital cases	There was no significant difference in the responses between the propofol and pentobarbital groups; however, the propofol group had a greater decrease in pulse rate and 3/31 (10%) patients had transient decreases in oxygen saturation <90%, with all responding to head repositioning, compared with the pentobarbital group that had 0 decrease in pulse oximetry levels <90%; the propofol group had a faster recovery than the pentobarbital group; the propofol group average time to arousal was 5 min and time to discharge 12.5 min; in the pentobarbital group, the average time to arousal was 21.5 min and time to discharge 34 min; both 100% effective	Radiology study; fasted patients; some difficulties with early randomization	Both propofol and pentobarbital are safe and effective for sedation for painless diagnostic studies, but require careful patient selection and diligent monitoring; pentobarbital had less decrease in pulse rate and less transient desaturation but had greater recovery time than propofol	II	II
Havel et al ⁷²	Prospective, blinded, randomized, controlled trial comparing IV midazolam and propofol for painful procedures in the ED; 46 patients in midazolam group: 0.1 mg/kg; 43 patients in propofol group: bolus 1 mg/kg, infusion 4–6 mg/kg/h; total of 89 patients; aged 9.0±3.8 y in propofol group, and 8.6±4.2 y in midazolam group	11.6% had oxygen saturation below 93%; no interventions were needed aside from oxygen; mean sedation 5.5/6 on Ramsay Sedation Scale	Sample size is only a minor limitation	Propofol is effective and safe; shorter recovery time than midazolam	I	I
Skokan et al ⁷³	Prospective observational study of ED procedures; 1-mg/kg dose followed by 0.5-mg/kg boluses; mean age 7.4 y; 40 patients	Oxygen administered by 2/3 physicians regardless of pulse oximetry levels; all patients received opiate as well; 30% required supplemental oxygen; 1 (2.5%) patient required brief bag-valve-mask ventilation; 100% rated sedation as excellent	Data collection very unclear; multiple variations in delivery and recording of information	Propofol is safe and effective for use in ED procedures	III	III
Hertzog et al ⁷⁴	Prospective observational study of propofol for oncology procedures in a pediatric ICU-affiliated procedural unit; 2-mg/kg bolus and additional intermittent bolus injections; efficacy was determined by the ability to complete hematology/oncology procedure; ages 7.5±4.3 y; 50 cases	4 (8%) transient pulse oximetry levels <92%, 1 patient required bag-valve-mask ventilation, 2 cases of transient apnea; 100% effective	No significant limitation	Propofol reasonable option for procedural sedation in pediatric ICU	Efficacy was not objectively measured	II

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Guenther et al ⁷⁵	Prospective observational study of procedural patients managed in a pediatric ED-associated sedation unit; patients electively scheduled for unit from multiple outpatient sources, most commonly hematology/oncology; protocol delivered propofol with fentanyl as 1–2 µg/kg; fentanyl initially, followed by 1 mg/kg of propofol; subsequent doses of 0.5 mg/kg administered at discretion of pediatric emergency physician managing sedation; mean dose 3.9 mg/kg of propofol; total of 87 patients underwent 291 separate sedations; efficacy defined as successful completion of procedure; 100% procedures successfully completed; median age 6 y	7% of children had transient desaturation below 90%, 4% partial airway obstruction requiring jaw thrust, 1% required transient bag-valve-mask assisted ventilation; transient decrease in systolic blood pressure noted with no clinical impact noted in almost all cases	Patients preselected and scheduled; success defined as completion of procedure with no adverse events	Propofol safe and effective for administration by pediatric emergency physicians in an ED-associated sedation unit	II	II
Bassett et al ⁷⁶	Prospective observational study of consecutive patients sedated with propofol in a pediatric ED; protocol delivered propofol with fentanyl as 1–2 µg/kg; fentanyl initially, followed by 1 mg/kg of propofol; subsequent doses of 0.5 mg/kg administered at discretion of pediatric emergency physician managing sedation; supplemental oxygen was applied to patients per protocol; mean dose 2.9 mg/kg of propofol; total of 392 patients underwent 393 separate sedations; median age 8 y	5% of children had transient desaturation below 90%, 3% partial airway obstruction, 0.8% required transient bag-valve-mask assisted ventilation; clinically insignificant transient decrease in systolic blood pressure noted in 84% of patients (median decrease 10.5 mm Hg); 6% demonstrated transient bradycardia with no clinical impact	No observations or definition of efficacy contained; conclusion that propofol is efficacious is stated and implied in lack of data that no procedures were not successfully completed	Propofol safe and effective when administered in ED setting	II	III
Jayabose et al ⁷⁷	Retrospective review of prospectively collected data on patients undergoing painful cancer-related procedures in an oncologic procedure unit; dosing varied depending on combination with other drugs; when only propofol was used the dosing was 25 mg/kg/min; age 2–15 y; 52 patients, 335 procedures	6 episodes of hypoxia <94%; no endotracheal tube intubations; efficacy on a unique scoring system was 93% for propofol only (160 episodes)	Some use of fentanyl, midazolam, and other agents	Propofol is safe and effective for use in patients undergoing painful procedures	III	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Keidan et al ⁷⁸	Prospective, randomized, controlled trial of propofol vs propofol/remifentanyl for bone marrow biopsy in outpatient clinic; 3-mg/kg bolus infusion of 18 mg/kg/h; 36 pure propofol patients; propofol group mean age 8.4±4.8 y; propofol/remifentanyl group mean age 9±5 y; 77 total patients	4 (11%) saturation <90%	May not be able to extrapolate from ASA III patients to ED	Propofol combined with remifentanyl is better than propofol alone	Efficacy was not objectively measured	II
Levati et al ⁷⁹	Prospective observational study of MRI patients in radiology suite; origin of patients from multiple clinical areas; 3.7- to 5.4-mg/kg propofol bolus (lower dose in weight >10 kg), 7.1- to 10.1-mg/kg/h infusion; efficacy was determined by the ability to complete MRI study; ages 2 wk to 11 y; 84 patients	No apnea, 5 (6%) ETCO_2 elevation, 1 hypoxia <97%; 100% effective	Some variation in monitoring in some patients	Propofol is useful and safe for painless diagnostic study such as MRI	II	II
Merola et al ⁸⁰	Retrospective review of anesthesia records of sedation for MRI; compared with chloral hydrate; unclear to what extent data were prospectively collected; 2 mg/kg bolus drip 80–140 $\mu\text{g}/\text{kg}/\text{min}$ (4.8–8.4 mg/kg/h); efficacy was determined by the ability to complete MRI study; ages 1 mo to 17 y; 318 propofol sedations; 455 total patients	No adverse outcomes documented; defined as pulse oximetry levels <94%	Unclear methods of data collection and documentation of adverse events	Propofol is reliable and safe	III	III
Scheiber et al ⁸¹	Retrospective chart review of prospectively collected data in children undergoing radiation therapy in radiology suite; sedated with 3.4 mg/kg bolus IV propofol, 7.6 mg/kg/h infusion; efficacy was determined by the ability to complete radiation therapy; mean age 30±7.8 mo; 11 patients underwent 155 sedative procedures	No saturation <92% on room air	Results not clearly documented; mean pulse oximetry levels reported; effective treatment	Sedation with propofol excellent method for radiotherapy	III	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade (Efficacy)	Grade (Safety)
Vardi et al ⁸²	Prospective, randomized, controlled trial of propofol vs ketamine for procedures in pediatric ICU; propofol dose 2.5–3 mg/kg bolus 12 mg/kg/h; ketamine dose 2 mg/kg plus midazolam 0.1 mg/kg plus fentanyl 2 µg/kg; mean age 7.25±5.73 y; 58 patients	For propofol sedation 9.6/10 scale and 5.6/6 on Ramsay Scale; for ketamine sedation 9.3/10 scale and 5.3/6 on Ramsay scale; for propofol: head repositioning 12 (20%), apnea requiring bag-valve-mask ventilation 10 (19%), no endotracheal tube intubations; for ketamine: airway repositioning 7 (14%), apnea 3 (6%), intubations 1 (2%)	May not be able to extrapolate from critically ill patients to stable ED patients	Both propofol and ketamine are safe and effective in pediatric ICU setting	III	III

IV, Intravenous; **ACTH**, adrenocorticotropic hormone; **IN**, intranasal; **IM**, intramuscular; **EEG**, electroencephalogram; **MPC**, meperidine-promethazine-chlorpromazine; **BM**, bone marrow; **prn**, as needed; **CHEOPS**, Children's Hospital of Eastern Ontario Pain Scale; **IQR**, interquartile range; **OR**, odds ratio; **NPO**, nothing by mouth.

APPENDIX A.

*Literature classification schema.**

Design/Class	Therapy [†]	Diagnosis [‡]	Prognosis [§]
1	Randomized, controlled trial or meta-analyses of randomized trials	Prospective cohort using a criterion standard	Population prospective cohort
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.

[†]Objective is to measure therapeutic efficacy comparing ≥ 2 interventions.

[‡]Objective is to determine the sensitivity and specificity of diagnostic tests.

[§]Objective is to predict outcome including mortality and morbidity.

APPENDIX B.

Approach to downgrading strength of evidence.

Downgrading	Design/Class		
	1	2	3
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X