

# Clinical Policy: Critical Issues in the Sedation of Pediatric Patients in the Emergency Department

**From the EMSC Panel (Writing Committee) on Critical Issues in the Sedation of Pediatric Patients in the Emergency Department:**

**Sharon E. Mace, MD, Chair, American College of Emergency Physicians (ACEP)**  
**Lance A. Brown, MD, MPH (ACEP)**  
**Lisa Francis, BSN, RN (Society of Pediatric Nurses)**  
**Steven A. Godwin, MD (ACEP)**  
**Sigrid A. Hahn, MD (ACEP)**  
**Patricia Kunz Howard, PhD, RN, CEN (Emergency Nurses Association)**  
**Robert M. Kennedy, MD (American Academy of Pediatrics)**  
**David P. Mooney, MD (American Pediatric Surgical Association)**  
**Alfred D. Sacchetti, MD (ACEP)**  
**Robert L. Wears, MD, MS, Methodologist (ACEP)**  
**Randall M. Clark, MD (American Society of Anesthesiologists)**

Other members of the EMSC Panel included:  
Ramon W. Johnson, MD (ACEP Board Liaison)  
Rhonda R. Whitson, RHIA (Clinical Policies Manager, ACEP)  
Tuei Doong (Vice President, The Nakamoto Group, Inc)  
Jenni Nakamoto-Yingling (President, The Nakamoto Group, Inc)  
Karen Belli (Public Policy and Partnerships Specialist, EMSC)  
Tasmeen Singh, MPH, NREMT-P (Executive Director, National Resource Center, EMSC)  
Tina Turgel (Nurse Consultant, EMSC)

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## PREFACE

Emergency physicians routinely provide sedation and analgesia, monitor the respiratory and cardiovascular status, and manage critically ill patients of all ages.<sup>1-3</sup> The provision of safe and effective sedation and analgesia is an integral part of emergency medicine practice and a component of the core curriculum for emergency medicine residency programs.<sup>4-6</sup> Failure to adequately treat a patient's pain can have negative consequences, the event potentially affecting later physiologic responses and behaviors. Appropriately treating pain and anxiety decreases patient suffering, facilitates medical interventions, increases patient/family satisfaction, improves patient care, and may improve patient outcome.<sup>7-10</sup>

Providing effective and safe procedural sedation in the emergency department (ED) is a multifactorial process beginning with the preprocedural patient assessment and continuing through intraprocedural monitoring and postprocedure evaluation. Setting up the proper environment and selecting the most appropriate pharmacologic and nonpharmacologic agents are keys to successful procedural sedation.<sup>1,11-15</sup> There are many drugs that can be used for procedural sedation and analgesia. In addition, there are various nonpharmacologic modalities that can be used for procedural sedation and analgesia.<sup>13-15</sup> The choice of a particular agent or modality is influenced by many factors.<sup>12</sup> These include patient characteristics (eg, age, comorbidity, special health care needs) and the procedure to be performed (painful or painless, duration, etc).<sup>12</sup> Appropriate monitoring and assessment are critical for safe and effective procedural sedation and analgesia.<sup>3,11,16,17</sup>

A previous clinical policy focused on medications for achieving sedation and analgesia in pediatric patients undergoing procedures in the ED.<sup>12</sup> This clinical policy deals with 2 additional sedation drugs, nitrous oxide and chloral hydrate; a nonpharmacologic agent for sedation, sucrose; as well as preprocedural fasting or *nulla per os* (NPO) status, and discharge criteria.

Multiple documents about procedural sedation have been issued by various professional organizations, including The Joint Commission, the American Academy of Pediatrics (AAP), the American Society of Anesthesiologists (ASA), and the American College of Emergency Physicians (ACEP).<sup>12,16-22</sup>

The goal of this panel is to eliminate the bias from the recommendations by creating a document that is, to the degree possible, evidence-based. With some aspects of procedural sedation, there is a relative deficiency of high-quality data.<sup>16</sup> This policy is not intended to set standards for individual institutions or practitioners and cannot address every topic about pediatric procedural sedation but does give data for answering key management issues using an evidence-based approach.

## INTRODUCTION

Procedural sedation is 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.<sup>16</sup> Analgesia is usually a component of procedural sedation particularly for painful procedures. Procedural sedation and analgesia yields a depressed level of consciousness while allowing the patient to maintain independent control of the airway and oxygenation by preserving the protective airway reflexes. Moderate sedation/analgesia, previously "conscious sedation," is a drug-induced depression of consciousness during which patients respond purposefully to verbal or light tactile stimulation while maintaining protective airway reflexes.<sup>18,20,22</sup> Deep sedation/analgesia is a drug-induced depression of consciousness during which patients are not easily aroused, and may need airway and/or ventilatory assistance but may respond purposefully to repeated or painful stimulation.<sup>19,20,22</sup> General anesthesia, in contrast, is a state of drug-induced loss of consciousness in which patients are not arousable and often have impaired cardiorespiratory function needing support.<sup>19,20,22</sup> The terminology "moderate sedation," "deep sedation," and "general anesthesia" may not apply to dissociative sedation. In dissociative sedation, as with ketamine, a trance-like cataleptic state occurs with both profound analgesia and amnesia while maintaining protective airway reflexes, spontaneous respirations, and cardiopulmonary stability.<sup>23</sup> In children, deep or dissociative sedation is usually required for painful procedures.<sup>24</sup>

Because individuals vary in their responses to a given dose of a specific sedative, practitioners providing procedural sedation and analgesia require the skills needed to provide airway/respiratory management and cardiovascular support. Health care providers administering procedural sedation/analgesia should be proficient in the skills needed to rescue a patient at a level greater than the desired level of sedation. Thus, if moderate sedation is desired, the practitioner should be able to provide the skills needed for deep sedation, and if deep sedation is intended, the practitioner should be competent in the airway management and cardiovascular support involved in general anesthesia.<sup>17</sup> Such skills are a requirement of emergency medicine training programs and an essential component of emergency medicine practice.<sup>3-5</sup>

## METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature. Multiple searches of MEDLINE and the Cochrane database were performed. Specific key words/phrases used in the searches are identified under each critical question. All searches were limited to English-language sources, human studies, and years 1976 to 2006. References obtained on the searches were reviewed by panel members (title and abstract) for relevance before inclusion in the pool of studies to be reviewed. Abstracts and articles were reviewed by panel members, and pertinent articles were selected.

These articles were evaluated, and those addressing the questions considered in this document were chosen for grading. Additional articles were reviewed from the bibliographies of studies cited. Panel members also supplied articles from their own knowledge and files.

The panel used the ACEP clinical policy development process; this policy is based on the existing literature; where literature was not available, consensus of panel members was used. The draft was sent to all of the participating organizations for comments during the expert review stage of development.

All articles used in the formulation of this clinical policy were graded by at least 2 panel members for strength of evidence and classified by the panel members into 3 classes of evidence on the basis of the design of the study, with design 1 representing the strongest evidence and design 3 representing the weakest evidence for therapeutic, diagnostic, and prognostic clinical reports, respectively (Appendix A). Articles were then graded on 6 dimensions thought to be most relevant to the development of a clinical guideline: blinded versus nonblinded outcome assessment, blinded or randomized allocation, direct or indirect outcome measures (reliability and validity), biases (eg, selection, detection, transfer), external validity (ie, generalizability), and sufficient sample size. Articles received a final grade (Class I, II, III) on the basis of a predetermined formula taking into account design and quality of study (Appendix B). Articles with fatal flaws were given an "X" grade and not used in the creation of this policy. Evidence grading was done with respect to the specific data being extracted and the specific critical question being reviewed. Thus, the level of evidence for any one study may vary according to the question, and it is possible for a single article to receive different levels of grading as different critical questions are answered. Question-specific level of evidence grading may be found in the Evidentiary Table available online at <http://www.annemergmed.com>, and online at <http://www.acep.org> on the Clinical Policies page.

Clinical findings and strength of 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 of 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 that are 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.

This policy is not intended to be a complete manual on pediatric sedation issues but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine.

It is the goal of the panel to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain enough quality information to answer a critical question, panel members believe that it is equally important to alert emergency physicians to this fact.

Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the emergency physician should consider. The panel clearly recognizes 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 crucial questions addressed in this policy.

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

**Inclusion Criteria.** This guideline applies to pediatric patients less than or equal to 18 years of age who are in a hospital ED and have conditions necessitating the alleviation of anxiety, pain, or both.

**Exclusion Criteria.** This guideline excludes patients greater than 18 years of age.

## CRITICAL QUESTIONS

1. **Should pediatric patients undergo a period of preprocedural fasting to decrease the incidence of clinically important complications during procedural sedation in the ED?**

### Patient Management Recommendations

**Level A recommendations.** None specified.

**Level B recommendations.** Procedural sedation may be safely administered to pediatric patients in the ED who have had recent oral intake.

**Level C recommendations.** None specified.

Key words/phrases for literature searches: preprocedural fasting, NPO, gastric emptying agents, vomiting, aspiration, procedural sedation.

Recommendations concerning preprocedural fasting in both pediatric and adult sedation are based on a rare but real risk of pulmonary aspiration. Definitive sedation guidelines based on sound evidence are lacking because of a paucity of ED studies about preprocedural fasting. The ASA fasting guidelines,

adopted by the AAP, are consensus-based, extrapolated from patients undergoing general anesthesia.<sup>25</sup> As noted in these guidelines, “Published evidence is silent on the relationship between fasting times, gastric volume, or gastric acidity and the risk of emesis/reflux or pulmonary aspiration in humans.” Although these recommendations may be appropriately cautious when considering patients who are undergoing elective general anesthesia, controversy exists as to whether these guidelines are applicable to the pediatric ED population.

An important distinction between procedural sedation and analgesia in the ED and general anesthesia in the operating room involves the preservation of airway reflexes. In moderate sedation, airway reflexes are generally maintained. These reflexes, although normally present, are less reliably maintained in deep sedation. However, in general anesthesia, airway reflexes are significantly blunted or completely suppressed, thus increasing the potential risk of aspiration.<sup>26-30</sup> Dissociative agents such as ketamine and inhalational agents such as nitrous oxide have a different mechanism of action and do not blunt the airway reflexes to the same degree as other sedatives. Therefore, the description for the continuum of sedation that ranges from anxiolysis to general anesthesia may not accurately reflect the minimal effect of these agents on protective airway mechanisms.

Aspiration is a rare but well-documented associated risk in patients undergoing general anesthesia. The incidence of aspiration in pediatric patients has been reported to be 1:978 and 1:2,632 patients in 2 pediatric specific studies by Warner et al<sup>28</sup> and Borland et al.<sup>29</sup> When both emergent and elective patients of all ages are reviewed, the incidence decreases to less than 1:3,500.<sup>30-32</sup> During emergency surgery, the incidence of reported aspiration increases to 1:895 in adults and general population patients<sup>27</sup> and as frequent as 1:373 patients in the Warner et al pediatric study.<sup>28</sup> The timing of reported aspiration events is most commonly seen during induction, laryngoscopy, and extubation (50% to 78%, 30% to 36%, and 4% to 33%, respectively), which does not apply to procedural sedation and analgesia.<sup>27-29</sup> Further, inhalational anesthetics can be emetogenic, with documented postoperative nausea and vomiting described in up to one third of all surgical patients.<sup>33,34</sup> In contrast, pediatric patients undergoing procedural sedation and analgesia are not intubated and have a much lower incidence of nausea and vomiting, varying from 0.3% to 10%.<sup>26,35-40</sup>

A significant relationship has been demonstrated to exist between aspiration during general anesthesia and the patient's ASA physical status.<sup>29</sup> Physical status classes of III and IV have been shown to have a significantly increased risk of aspiration compared to that of ASA I and II patients (1:418 versus 1:1,341).<sup>29</sup> Warner et al<sup>28</sup> found a greater safety range, with only a 1:7,945 risk of aspiration in pediatric patients with ASA I and II physical status classes. The majority of reported pediatric ED procedural sedation and analgesia occurs in a healthier

patient population, classified as ASA physical status I or II.<sup>26,30,37-39,41,42</sup>

Documentation of clinically significant or subclinical aspiration events during procedural sedation and analgesia is extremely limited. Only 1 study reports any incidents of aspiration.<sup>43</sup> The adverse event occurred in 2 pediatric patients, both of whom met NPO criteria for fasting. These patients were deeply sedated with opioid-barbiturate combinations, one for a radiologic procedure and the other for bronchoscopy. Both required only supplemental oxygen and observation. A review of the literature reveals no other reported cases of aspiration as a result of procedural sedation and analgesia in the ED. Given the rare occurrence of aspiration, to date no single study is adequately powered to determine the incidence of aspiration during ED procedural sedation.

Multiple factors have been investigated in an attempt to identify risk factors for aspiration in the general anesthesia population. These questions include the relationship between aspiration and gastric contents, motility, and acidity. To date, no benefit from the routine addition of antacids and other pharmacologic motility regimens preoperatively has been demonstrated.<sup>25,32</sup>

Concerning NPO status, 2 Class I<sup>44,45</sup> and 2 Class II studies<sup>46,47</sup> evaluated gastric fluid volume and pH after various fasting periods. In one of the Class I studies, Maekawa et al<sup>44</sup> found no difference in gastric fluid volume, pH, lipid homeostasis, or glucose levels with NPO periods of 2, 4, and 12 hours after drinking apple juice. The other Class I study compared NPO after midnight with clear liquids up to 3 hours preoperatively and demonstrated no difference between groups' gastric fluid volume or pH.<sup>45</sup> These findings are supported by a Class II study by Ingebo et al<sup>46</sup> that used endoscopic suction after intravenous sedation. The duration of fasting after clear fluid ingestion ranged from 0.5 to 24 hours, with a mean period of 6.7+/-5.3 hours. There was no significant difference in gastric fluid volumes or pH between the groups with the following fasting times: 30 minutes to 3 hours, more than 3 hours to 8 hours, and more than 8 hours.<sup>46</sup>

There are limited data about clearance of solids alone. A Class II adult study evaluated 8 healthy adult female volunteers who received a light meal and underwent gastric ultrasonography, followed by nasogastric placement for gastric volume monitoring.<sup>47</sup> A gastric emptying study with paracetamol was then performed. Although 3 patients cleared 120 minutes after the meal, it took 240 minutes for all patients to be solid free.

A total of 8 studies were found that evaluated the effect of fasting versus nonfasting on adverse events in pediatric patients undergoing procedural sedation.<sup>26,35,37,38,42,43,48,49</sup> Five Class II<sup>26,35,37,42,43</sup> and 3 Class III<sup>38,48,49</sup> studies evaluating NPO status were reviewed. These studies recorded a total of 4,814 patient encounters, with 2 documented episodes of clinically apparent pulmonary aspiration. As noted above by Hoffman et al,<sup>43</sup> both of these patients were fasted. On pooling of these

data, the incidence of clinically apparent pulmonary aspiration during sedation may reflect an incidence of less than 1:2,000 pediatric patient encounters.

Two studies evaluated the NPO status for solids and liquids. In a Class II study by Agrawal et al,<sup>26</sup> only 44% (396/905 patients) met published ASA/AAP guidelines. There was no significant difference in adverse events, including emesis, between patients meeting or not meeting established guidelines. The median time for fasting duration in patients with emesis was 6.8 hours (interquartile range [IQR] 5.1 to 9.5 hours) for solids and 5.8 hours (IQR 3.6 to 8.1 hours) for clear liquids. Median fasting duration for solids increased with age and ranged from 4.2 hours (IQR 2.4 to 6.3 hours) in patients younger than 6 months (n=14) to 7.3 hours (IQR 5.5 to 9.7 hours) in patients older than 36 months (n=644). The median fasting duration for clear liquids also increased with age. The duration increased from 4.1 hours in patients younger than 6 months (IQR 2.4 to 6.3 hours) to 6.4 hours (IQR 4.4 to 8.6 hours) in patients older than 36 months. The authors suggested that given that 56% of patients did not meet criteria and no increase in adverse events was found, that noncompliance with ASA/AAP guidelines does not appear to be a contraindication for procedural sedation.<sup>26</sup> In another Class II study, Babl et al<sup>35</sup> identified 155 of 220 children (71.1%; 95% confidence interval [CI] 64.5% to 77.0%) who did not meet fasting guidelines for solids. Thirty-seven (20.6%; 95% CI 15.0% to 27.3%) children did not meet fasting guidelines for clear liquids. The median fasting duration was 4.4 hours (IQR 3 to 6.5 hours) for solids and 4 hours (IQR 2.2 to 6.3) for liquids. Again, there was no significant difference in emesis rate between patients meeting and not meeting fasting guidelines.<sup>35</sup>

Few patient data sets are available with numbers involving fasting of less than 2 hours. In a Class II study involving a pediatric ED sedation databank, authors extracted data about fasting status, sedation, and adverse events.<sup>37</sup> The fasting time was documented in 1,555 of 2,085 (74.6%) patients. Median fasting time before sedation was 5.1 hours (range 5 minutes to 32.5 hours). No significant difference was found in adverse events when patients were compared with fasting times in 2-hour time blocks up to greater than 8 hours (0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, >8 hours, and undocumented). A total of 156 of 1,555 (7.5%) patients experienced emesis. One hundred fifty patients were fasted for less than 2 hours, with 10 (6.7%) of these patients experiencing emesis. A total of 391 patients were fasted for 2 to 4 hours, with 40 (10.2%) episodes of documented emesis.<sup>37</sup> In a Class III study of children undergoing echocardiography, 334 children were divided into 2 groups treated with chloral hydrate.<sup>48</sup> The first group of 140 patients was fasted for less than 2 hours, with a mean of 80 minutes. A second group of 184 patients was fasted for greater than 2 hours, with a mean of 225 minutes. There were no major adverse outcomes in either group, as well as no differences in rates of emesis between groups ( $P=.74$ ).

Patients less than 6 months of age who were fasted for greater than 2 hours experienced a significantly higher incidence of inadequate sedation ( $P=.03$ ) than patients fasted for less than 2 hours.<sup>48</sup> In a Class III study, Keiden et al<sup>49</sup> evaluated children undergoing a hearing test who were sedated with chloral hydrate. This retrospective cohort study extracted data from 2 hospitals using different fasting guidelines. At one hospital (group 1), fasting guidelines were strictly enforced, whereas the second hospital (group 2) enforced no fasting guidelines prior to sedation. The average fasting period was significantly longer in patients with strictly enforced fasting guidelines than in the second group of patients who had no fasting guidelines (5.7 +/- 1.7 versus 2 +/- 0.2 hours;  $P<0.001$ ). Patients who followed fasting guidelines demonstrated a significantly higher failure rate in achieving sedation with an equivalent first dose of chloral hydrate compared with the second group of unfasted patients (21% versus 11%;  $P=0.03$ ). The higher failure rate resulted in patients requiring higher medication dosages (83 +/- 31 versus 61 +/- 21 mg/kg;  $P<0.01$ ) for adequate sedation and remaining sedated for longer periods (103 +/- 42 versus 73 +/- 48 minutes;  $P<0.001$ ), resulting in a later discharge.<sup>49</sup>

As previously noted, the only documented cases of aspiration were discussed in a Class II study by Hoffman et al.<sup>43</sup> In this study, however, adherence to NPO guidelines did not affect overall risk of complications (11 of 309 NPO guidelines followed [3.6%], 95% CI 1.8% to 6.2% versus 29 of 651 NPO guidelines not followed [4.5%], 95% CI 3.0% to 6.3%; odds ratio [OR] 0.79;  $P=.64$ ) and did not decrease the risk of hemodynamic and respiratory complications (9 of 309 NPO guidelines followed [2.9%], 95% CI 1.3% to 5.5% versus 18 of 651 NPO guidelines not followed [2.8%], 95% CI 1.6% to 4.3%; OR 0.97; NS). The complication risk was insignificantly different in patients without documented NPO status (3 of 45 [6.7%], 95% CI 1.4% to 18.3% versus 37 of 915 [4.0%], 95% CI 2.9% to 5.5%; OR 1.68;  $P=.43$ ). The occurrence of sedation failures was significantly higher in patients who met NPO criteria (20 of 921 [2.2%], 95% CI 1.3% to 3.3% versus 2 of 443 [0.5%], 95% CI 0.05% to 1.6%; OR 4.4;  $P=.016$ ). The authors suggest that this loss of effective sedation may be a result of increased agitation as a result of hunger in these children.<sup>43</sup>

In conclusion, there is no evidence suggesting a correlation between fasting, emesis, and pulmonary aspiration in healthy pediatric patients undergoing procedural sedation in the ED. Overall it is important to note that although many studies do include patients who were not fasted before their procedure, it is possible that clinicians may have been considering other undisclosed factors that selectively affect NPO times prior to procedural sedation. This selection bias is difficult to identify in the studies but may more closely represent current clinical practice.

Given the many variables present even in the best-designed studies, clinical judgment should always weigh the risk and benefits for each patient.<sup>50</sup>

## 2. Is nitrous oxide effective and safe for providing pediatric procedural sedation in the ED?

*A previous clinical policy focused on the efficacy and safety of etomidate, fentanyl/midazolam, ketamine, methohexital, pentobarbital, and propofol for achieving sedation and analgesia in pediatric patients undergoing procedures in the ED.<sup>12</sup> See Appendix C for the recommendations from the previous clinical policy.*

### Patient Management Recommendations for Nitrous Oxide

**Level A recommendations.** Nitrous oxide at 50% concentration can be used with concurrent local anesthesia for safe and effective procedural sedation in healthy children undergoing painful procedures.

**Level B recommendations.** A gas scavenging system should be used for protection of health care providers when administering nitrous oxide.

#### Level C recommendations.

- (1) Nitrous oxide at 60% to 70% concentration may be used with concurrent local anesthesia for safe and effective procedural sedation in healthy children undergoing painful procedures.
- (2) Nitrous oxide may be combined with other sedative analgesic agents to augment sedation, but patients receiving these combinations should be carefully monitored for deepening sedation, respiratory depression, and other adverse events.
- (3) Nitrous oxide may be less effective in reducing procedure-related distress in younger children compared with older children.
- (4) Nurses trained in principles of nitrous oxide sedation, including the specific nitrous oxide administration device, may safely administer nitrous oxide to healthy children while under the supervision of an emergency physician or other appropriately trained and credentialed specialist in the ED.

The evidentiary basis for the efficacy and safety of a given drug may differ. Considering that significant adverse events are generally rare, it is likely that there is stronger evidence for efficacy than for safety. When assigning one overall recommendation for a given drug based on combining these 2 distinct attributes (efficacy and safety) of the drug, the lowest most conservative level of evidence has been designated.

#### Efficacy of Nitrous Oxide

Key words/phrases for literature searches: nitrous oxide, procedural sedation; age 1-18 years.

Nitrous oxide (N<sub>2</sub>O) is a relatively weak dissociative anesthetic gas that provides mild to moderate procedural anxiolysis, analgesia, and amnesia in a linear dose-response pattern.<sup>51</sup> When used for sedation, N<sub>2</sub>O is blended with oxygen (N<sub>2</sub>O/O<sub>2</sub>) and generally denoted, as in this guideline, as N<sub>2</sub>O, without acknowledgment of the O<sub>2</sub> blend. Use of local anesthesia and imagery to prepare patients for the gas's clinical

effects, eg, imagining flying, significantly enhances the drug's efficacy.<sup>52</sup> N<sub>2</sub>O has both opioid agonist and *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist effects.<sup>53,54</sup> In healthy patients, N<sub>2</sub>O has minimal cardiovascular or respiratory effects;<sup>55-57</sup> however, it may enhance the depressed response to hypoxia and hypercarbia induced by other agents.<sup>55-59</sup> Onset and offset of effects occur within 5 minutes, and N<sub>2</sub>O does not require vascular access or painful administration.

For more than a century and with few adverse events, 30% to 70% N<sub>2</sub>O has been widely used to reduce distress in children during dental procedures.<sup>60</sup> A 50% concentration of N<sub>2</sub>O has also been used for management of acute pain in adults in out-of-hospital and ED settings.<sup>61,62</sup> The demand valve-equipped fixed 50% N<sub>2</sub>O delivery apparatus commonly available in EDs is difficult for children to activate, but patients of all ages easily use the continuous-circuit devices, some of which deliver up to 70% N<sub>2</sub>O.<sup>63</sup>

Numerous studies in children undergoing dental procedures in dental offices detail the effectiveness of N<sub>2</sub>O in reducing anxiety and distress,<sup>64-71</sup> but relatively few studies have been conducted in children undergoing painful procedures in the ED. Sixty-one articles concerning use of nitrous oxide for procedural sedation in children were identified. Local anesthesia was routinely used as an adjunct. After grading, 44 articles were included in this analysis.

Suturing-related distress in children was reduced by N<sub>2</sub>O in 2 Class I,<sup>72,73</sup> 2 Class II,<sup>74,75</sup> and 1 Class III<sup>76</sup> ED-based studies. Luhmann et al<sup>72</sup> found that children aged 2 to 6 years had lower distress scores during wound cleaning, supplemental lidocaine injection, and suturing when they received 50% N<sub>2</sub>O instead of oral midazolam in addition to standard topical anesthetic, video cartoon viewing, and bedside parent. Combining midazolam with N<sub>2</sub>O did not further reduce distress. Children who received N<sub>2</sub>O alone were less likely to experience minor adverse effects (ataxia, dizziness, crying), other than vomiting, in the ED and within 24 hours. Vomiting occurred more frequently with N<sub>2</sub>O (10% with N<sub>2</sub>O, 2% with N<sub>2</sub>O+midazolam). Burton et al<sup>73</sup> also found reduced distress with 50% N<sub>2</sub>O during suturing. Gamis et al,<sup>74</sup> using 30% N<sub>2</sub>O, found less distress with N<sub>2</sub>O in children older than 8 years but only a trend in that direction in younger children.

Distress during fracture reduction in children was also reduced with use of N<sub>2</sub>O in 1 Class I study,<sup>77</sup> 4 Class II studies,<sup>78-81</sup> and 1 Class III<sup>82</sup> study conducted in the ED or orthopedic clinic. Luhmann et al<sup>77</sup> found that N<sub>2</sub>O+lidocaine hematoma block (HB) for fractures was as effective in reducing distress as intravenous ketamine during forearm fracture reductions in children aged 5 to 17 years. Recovery was much faster for N<sub>2</sub>O+HB (16 minutes versus 83 minutes). Comparable decreases in distress during fracture reduction with 50% N<sub>2</sub>O were also found versus intravenous regional anesthesia<sup>79</sup> or intramuscular meperidine and promethazine.<sup>78</sup> Hennrikus et al<sup>80</sup> and Wattenmaker et al<sup>82</sup> noted decreased

levels of distress with 50% N<sub>2</sub>O alone. Hennrikus et al<sup>81</sup> found that subsequent addition of a HB further reduced distress.

Use of N<sub>2</sub>O also reduced children's distress during other painful procedures such as lumbar puncture, abscess drainage, cyst/nevi excision, bone marrow aspiration, dressing change, and intravenous catheter placement in 6 Class II<sup>64,75,83-86</sup> studies and 1 Class III<sup>87</sup> study conducted in various outpatient settings. Recovery from N<sub>2</sub>O sedation, when noted, was reported to be very rapid.<sup>71-73,75,77-79,88</sup>

Depth of sedation with a specific concentration of N<sub>2</sub>O may vary.<sup>89</sup> In a Class II study, Babl et al<sup>35</sup> found that with 50% to 70% N<sub>2</sub>O, 86% of children were moderately, 7% deeply, and 7% poorly sedated during ED procedures. A Class I study by Burton et al<sup>73</sup> found deep sedation in 12% of children during suturing, and a Class I study by Luhmann et al<sup>77</sup> and Class II studies by Hennrikus et al<sup>80,81</sup> found 2% to 9% of children poorly sedated with 50% N<sub>2</sub>O during fracture reduction. Sedation also may significantly deepen when other sedative or analgesic agents are co-administered with N<sub>2</sub>O. Several studies noted as secondarily observed outcomes, that although N<sub>2</sub>O was still effective when compared with placebo, increasing distress was observed with decreasing age, especially in children less than 6 to 8 years of age.<sup>69,74,86,87</sup> The relationship between effectiveness of N<sub>2</sub>O and age needs further evaluation using continuous-circuit devices easily used by young children.

#### Safety of Nitrous Oxide

Key words/phrases for literature searches: nitrous oxide, procedural sedation; age 1-18 years.

When N<sub>2</sub>O was used alone or in combination with local anesthesia in healthy (ASA Physical Status class I and class II) children, no major cardiopulmonary adverse events (apnea, significant hypoxia, hypotension, or bradycardia) were reported in the studies examined, including two<sup>35,90</sup> in which 50% to 70% N<sub>2</sub>O without additional systemic sedative or analgesic medication was administered by specially trained nurses to ASA I or II ED patients.<sup>35,64-66,68,70-96</sup> A Class III report summarizing patient data sheets on 35,828 administrations of N<sub>2</sub>O, 82% of which were given to children, found that 9 (0.03%) serious adverse events (somnolence, vomiting, bradycardia, vertigo, headache, nightmares, sweating) were possibly attributed to the 50% N<sub>2</sub>O.<sup>97</sup> However, no clinical information about these cases was presented, nor about 18 others with more serious events (apnea, desaturation, laryngospasm, convulsions, and a cardiac arrest) thought not to have been caused by the N<sub>2</sub>O. Deaths associated with N<sub>2</sub>O use have been due to inadvertent administration of 100% nitrous oxide, with subsequent hypoxia. As reviewed by Duncan and Moore,<sup>98</sup> these tragedies point out the essential need for clinicians to understand all aspects, including mechanical, of the gas delivery device being used.

No study was large enough to determine the risk of clinically significant pulmonary aspiration during inhalation of N<sub>2</sub>O, because of the rarity of this event. Focused attempts to answer

this question found no radiopaque dye on chest radiograph after the dye was placed in the posterior pharynx of 50 children undergoing dental procedures with 20% to 65% N<sub>2</sub>O<sup>95</sup> or in 14 adult volunteers sedated with 50% N<sub>2</sub>O for 5 minutes.<sup>91</sup> However, traces of dye were found on chest radiograph in 2 of 10 volunteers sedated with 50% N<sub>2</sub>O for more than 10 minutes. The clinical significance of this micro-aspiration is unclear.<sup>96</sup> Whether the combination of N<sub>2</sub>O with other sedative or analgesic medications increases the risk for aspiration and other adverse events is unknown.

Emesis was the most common adverse event reported. In 2 Class I,<sup>72,77</sup> 6 Class II,<sup>35,73,74,79-81</sup> and 1 Class III<sup>78</sup> trials, the frequency of emesis with 50% N<sub>2</sub>O varied from a high of 26% (6% during the procedure) when co-administered with oral oxycodone<sup>77</sup> to 10%,<sup>72</sup> 6%,<sup>73</sup> or none when administered alone.<sup>74,78-81</sup> No clinically apparent aspiration was noted in these studies. Babl et al<sup>35</sup> found that vomiting occurred in 7% of pediatric patients during N<sub>2</sub>O administration in the ED. Emesis did not appear to be associated with the length of fasting, type of procedure, depth of sedation, or length of administration. Other commonly reported minor adverse effects include nausea, dizziness, euphoria, and dysphoria.<sup>35,72,73,77,87,99</sup> Most reported resolution of these effects within 5 minutes of cessation of N<sub>2</sub>O administration.

Hypoxemia was found to occur rarely with N<sub>2</sub>O administration in healthy patients, in part because N<sub>2</sub>O was blended with oxygen. When end-tidal carbon dioxide (ETCO<sub>2</sub>) was measured, mild respiratory depression was found to occur when N<sub>2</sub>O was co-administered with other sedative or analgesic medications. Class II safety studies conducted in the operating room prior to general anesthesia noted increasing ETCO<sub>2</sub> with increasing concentrations of N<sub>2</sub>O in children who had also received oral chloral hydrate<sup>57</sup> or oral midazolam 0.7 mg/kg<sup>56</sup> but not 0.5 mg/kg.<sup>55</sup> These studies are consistent with the finding that young children sedated with oral midazolam 0.5 mg/kg+50% N<sub>2</sub>O for facial laceration repair had no significant respiratory effects.<sup>72</sup> Although there have been concerns about diffusion hypoxia with cessation of N<sub>2</sub>O administration, in a Class II study, comparison of room air versus O<sub>2</sub> for "wash out" after 30 minutes of 40% N<sub>2</sub>O found no clinically significant difference in oxygen saturations.<sup>93</sup> Finally, studies in healthy children undergoing elective dental procedures found no significant adverse events when N<sub>2</sub>O was combined with other low-dose sedative medications;<sup>64,66,68</sup> it is not clear whether these medication combinations are safe for procedural sedation in children in the ED.

Chronic exposure to environmental N<sub>2</sub>O may have adverse effects on health care providers, but infrequent brief contact with N<sub>2</sub>O is likely safe for individual patients, with the exception of rare patients deficient in enzymes associated with methionine synthesis or deficient in vitamin B<sub>12</sub>, in whom N<sub>2</sub>O may cause central nervous system injury.<sup>100</sup> A Class III survey of female dental assistants found 60% reduction in fertility with greater than 5 hours per week of exposure to unscavenged N<sub>2</sub>O;

no effect was found if the N<sub>2</sub>O was scavenged.<sup>101</sup> Subsequent analysis of that data also found a relative risk of 2.6 for spontaneous abortion if female dental assistants were working with unscavenged N<sub>2</sub>O.<sup>102</sup> A Class III survey of midwives found no association between N<sub>2</sub>O use at delivery and fertility except in those assisting at greater than 30 deliveries a month.<sup>103</sup> No association was found with spontaneous abortions.<sup>104</sup> Another Class III survey of dentists and their assistants found that users with “heavy exposure” to N<sub>2</sub>O were more likely to report numbness, tingling, or muscle weakness.<sup>105</sup>

### 3. Can oral sucrose be used to reduce infant distress due to minor, painful procedures in the ED?

#### Patient Management Recommendations

**Level A recommendations.** Oral sucrose can be used to reduce signs of distress due to minor, painful procedures in preterm and term neonates (less than 28 days old).

#### Level B recommendations.

- (1) Effective doses for neonates range from 0.1 mL of 24% to 2 mL of 50% sucrose (with the most commonly studied dose being 2 mL of 24% sucrose).
- (2) Oral sucrose can be used in combination with sucking (ie, a pacifier) to improve its efficacy.
- (3) Oral sucrose may be safely administered to full-term neonates and infants.

#### Level C recommendations.

- (1) Sucrose appears to be less effective in infants between 1 month and 6 months of age.
- (2) Effective doses for infants between 1 month and 6 months of age may range from 0.75 mL of 50% to 2 mL of 75% sucrose.
- (3) Effective doses for very-low-birth-weight, preterm infants may be as low as 0.05 mL of 24% sucrose.
- (4) Oral sucrose should be given approximately 2 minutes before an invasive procedure.
- (5) Oral sucrose may be safely given to low-birth-weight, preterm neonates.

Key words/phrases for literature searches: sucrose, behavioral distress, pain, infants, neonates, procedural sedation; age 0-1 year.

Sucrose has been widely studied as a nonpharmacologic intervention to reduce pain in young infants undergoing minor, invasive procedures. The AAP, in their guideline “The Relief of Pain and Anxiety in Pediatric Patients in Emergency Medical Systems,” recommends that oral sucrose be used as an adjunct for limiting procedural pain in neonates and infants younger than 6 months of age, and suggests that it may be more effective when given in combination with a pacifier.<sup>106</sup> The Cochrane Collaboration performed a systematic review of the topic for neonates and concluded that sucrose is safe and effective for reducing pain caused by a single, painful event (eg, heel lance or venipuncture).<sup>107</sup>

Despite a large body of literature published on the subject,

there are still a number of unanswered questions about the use of sucrose for pain relief in infants. Biological and contextual factors affect sucrose’s effectiveness and contribute to difficulty in determining the optimal dose and effect magnitude. Patient factors include the infant’s gestational age and postnatal age, baseline level of alertness, overall health, and previous painful experiences. Contextual factors include comfort measures used along with sucrose during the procedure, such as holding by a nurse or parent or using pacifiers. The “pharmacologic” variables related to sucrose involve not only the concentration and volume given but also the method of administration (by syringe or pacifier and whether on the anterior or posterior tongue), frequency of administration, and time of administration before the painful procedure. Questions also remain about the efficacy of sucrose in older infants. Published trials have most commonly enrolled preterm and term neonates. Fewer studies have included older infants, limiting the conclusions that can be drawn about this group. It is also unclear how well findings from the commonly studied neonatal intensive care unit (NICU) or well-baby population extrapolate to the ED; only 1 trial actually took place in the ED.<sup>108</sup> The ED generally sees an overall healthier population, with fewer preterm infants than the NICU, but, unlike the well-baby nursery, sees infants with acute illnesses. Additionally, the painful stimulus studied in some trials is not relevant to the ED (eg, circumcision), whereas other common ED procedures, such as bladder catheterization or lumbar puncture, were rarely or never evaluated.

Some uncertainty is also inherent in the measurement of an infant’s perception of pain. Most studies measured various behavioral or physiologic markers of distress or a combination thereof. A commonly used outcome measure is infant crying, which has intuitive “face validity.” However, the best quantitative measure of crying (percentage of time crying, duration of the cry, total time crying, etc) has yet to be determined. Vital signs have also been used. For example, tachycardia and a decrease in oxygen saturation have been identified as indirect evidence that pain is occurring.<sup>109</sup> Physiologic variables may be affected by many factors other than pain and are therefore nonspecific. In an attempt to improve the sensitivity, reliability, and validity of infant pain assessment, numerous composite measures incorporating behavioral, physiologic, and contextual markers have been developed and validated. Validated composite scales that were used in the trials reviewed in this section include the Neonatal Infant Pain Scale (NIPS),<sup>110</sup> the Neonatal Facial Coding Scale (NFCS),<sup>111</sup> the Douleur Aigue chez le Nouveau-ne (DAN),<sup>112</sup> and the Premature Infant Pain Profile (PIPP),<sup>113</sup> the latter of which takes gestational age into account. Overall, the heterogeneity of outcome measures used, variability regarding when the measurements are taken (during or after the procedure), and the variable reliability of the measures themselves have made direct comparisons among studies difficult.

The following discussion reviews the published literature to

determine the efficacy of oral sucrose in reducing signs of pain or distress in infants. Overall, studies were well-designed, randomized controlled trials that were blinded unless precluded by the intervention. Many had fairly small sample sizes (<100 infants), resulting in wide CIs, and limiting external validity. Studies were downgraded for various methodological weaknesses, as detailed in the Evidentiary Table (available online at <http://www.annemergmed.com>, and online at <http://www.acep.org> on the Clinical Policies page), or if their design did not directly answer the critical question. Although glucose, breast milk (which contains 7% lactose), and some nonsucrose sweeteners may also act through the same mechanism, this discussion is limited to sucrose.

#### Efficacy of sucrose in neonates

The Class I Cochrane meta-analysis calculated a weighted mean difference (WMD) and CI for several outcome measures.<sup>107</sup> PIPP scores were pooled for 3 studies that used doses ranging from 0.1 mL to 0.5 mL of 24% sucrose.<sup>114-116</sup> PIPP scores can range from 0 (no pain) to 18 for term, or 21 for preterm, infants (maximal pain). The WMD was highly statistically significant for sucrose relative to control at 30 seconds (-1.64; 95% CI -2.47 to -0.81;  $P=0.0001$ ) and 60 seconds after heel stick (-2.0; 95% CI -3.08 to -1.05;  $P=0.0001$ ). The authors also pooled data for change in heart rate from 2 studies and found that there was no significant change with doses ranging from 2 mL of 25% to 30% sucrose at 1 minute (WMD 0.90; 95% CI -5.81 to 7.61) or 3 minutes (WMD -6.20; 95% CI -15.27 to 2.88) after heel stick.<sup>117,118</sup> Results for preterm and term infants were not considered separately in this systematic review.

Ten Class II, randomized, controlled trials evaluated the effect of sucrose on behavioral and/or physiologic indicators of pain, or composite pain scores, in full term neonates. Results of both primary and secondary outcome measures are described here.<sup>117-126</sup> Although some of the trials below had multiple treatment arms in addition to sucrose, only comparisons of sucrose versus water or placebo are described. The majority of trials found a reduction in crying in the sucrose group during heelstick or venipuncture,<sup>117,119-122</sup> whereas a minority found no effect.<sup>123,124</sup> Pain scores (including DAN and facial expression scores) were lower in the sucrose group in some trials<sup>124,125</sup> but not in others.<sup>118,120</sup> Response of vital signs to painful stimulus was variable; some trials found a decrease in heart rate in the sucrose group,<sup>119,122</sup> but most trials found no consistent difference in heart rate,<sup>117,120,126</sup> respiratory rate,<sup>119</sup> SaO<sub>2</sub>,<sup>118,119</sup> or vagal tone<sup>120,121</sup> among treatment groups.

Five Class II trials looked at sucrose in preterm infants. Crying time was consistently reduced with sucrose in this age group.<sup>127-131</sup> Three trials that evaluated behavior using the NFCS or a "composite behavioral scale" found that scores were lower in the treatment group.<sup>128,130,131</sup> Physiologic effects again were mixed; several studies found a lower heart rate<sup>128,129</sup> and respiratory rate<sup>129</sup> in the treatment group, whereas others found

no effect on heart rate,<sup>127,131</sup> SaO<sub>2</sub>,<sup>128,129</sup> or cerebral blood flow.<sup>129</sup> An additional 11 Class III studies investigating the analgesic efficacy with various invasive procedures in term and/or preterm infants were identified.<sup>114,132-141</sup> Most found some reduction in measures of distress caused by painful procedures.

#### Efficacy in older infants

Fewer studies have evaluated the analgesic effect of sucrose in older infants. Overall sucrose appears to be less effective than in neonates, but there may be a modest reduction in crying time with higher doses of sucrose in 2-, 4-, and 6-month-olds. Three Class II trials evaluated sucrose for intramuscular vaccinations in an outpatient setting.<sup>123,142,143</sup> Barr et al<sup>142</sup> compared 0.75 mL of 50% sucrose versus water in infants receiving intramuscular immunizations at 2 months of age and then again at 4 months. They found no difference in percentage of time spent crying during injection, but a smaller percentage of time crying during the 60 seconds after injection in the sucrose group (69% versus 83%;  $P<0.05$ ). In another study, Lewindon et al<sup>143</sup> compared an unusually high concentration of sucrose (2 mL of 75%) against water in 2-, 4-, and 6-month-olds. Mean total crying time was reduced from 59 to 36 seconds ( $P=0.00008$ ) and mean first cry duration decreased from 42 to 29 seconds ( $P=0.0004$ ) in the sucrose group. Of interest, although nurses perceived infant distress to be lower in the sucrose group, parents did not perceive a difference in the level of infant distress between the 2 groups. Allen et al,<sup>123</sup> on the other hand, found no difference in crying time between the 12% sucrose group versus water in *any* age category (2 weeks to 18 months). Another study, which differed from the others in that it compared 25% sucrose plus nonnutritive sucking, plus holding against control, found that total crying time and first cry duration were reduced in the treatment group, but there was no effect on heart rate.<sup>144</sup> Parents preferred the intervention, and nurses found the intervention to be no more difficult than control.

The only trial to take place in the ED enrolled infants less than 91 days of age who required bladder catheterization during their evaluation.<sup>108</sup> In this Class II trial, there was no difference between the placebo and 24% sucrose for any of the 3 primary outcome measures: composite behavioral scale (DAN score), percentage of infants crying during catheter insertion, and time to return to behavioral baseline. A post hoc subgroup analysis found a difference in the neonates but no difference in the 31- to 60- and 61- to 90-day age groups. The duration of the painful procedure was considerably longer than the noxious stimuli evaluated in the other studies and may have affected the observed efficacy of sucrose.

#### Dose of sucrose

Several studies have directly compared the efficacy of various doses of sucrose. In a Class II trial, Abad et al<sup>127</sup> found a reduction in crying from 63 seconds in the 12% group to 19 seconds in the 24% group (versus 73 seconds in controls;

$P=0.0256$ ). In another Class II trial, Haouari et al<sup>118</sup> compared 2 mL of 12.5%, 25%, and 50% sucrose in full-term infants and found a significant reduction in the primary outcome measure, postprocedural crying time, only in the 50% group versus controls ( $P=0.02$ ). Blass and Shah,<sup>145</sup> in a Class III study, compared a range of sucrose doses, 2 mL of 6%, 12%, and 17%, given over 2 minutes before heel stick. Looking at crying per unit time, they found no dose-response curve. Guala et al,<sup>126</sup> in a Class II trial, compared 33% and 50% sucrose in full-term infants and found no difference in heart rate. Ramenghi et al<sup>139</sup> compared 25% and 50% sucrose (among other interventions) in a Class III trial and found that although sucrose was superior to water in reducing crying time and behavior scores, there was no difference in efficacy between the 25% and 50% groups. Thus, these individual trials did not show consistent evidence of a dose-response curve, although the higher doses more consistently had a positive effect. Unfortunately, as the authors of the Cochrane review note, the inconsistency of dosing across trials (both in amount and concentration given) preclude pooling of data to determine the minimal effective or optimal dose of sucrose.<sup>107</sup> Doses investigated and found to be effective in older infants were generally higher than those in neonates.

#### Timing of sucrose administration

Only 1 trial was specifically designed to evaluate the optimal timing of sucrose administration before a procedure. In this Class III study, Blass and Shah<sup>145</sup> compared 2 mL of 12% sucrose at 30, 60, 90, 120, and 240 seconds before heel stick. The study included healthy newborns, but the number of subjects enrolled in this subsection of this 2-part study was not clearly stated. The group given sucrose 120 seconds before the procedure cried significantly less than all other groups ( $P<0.03$ ). Most subsequent studies have administered sucrose approximately 2 minutes before the invasive procedure.

#### Efficacy in combination with other comfort measures

In many of the studies evaluating the efficacy of sucrose, 1 or more of the arms included other non-pharmacologic comfort measures, such as a pacifier or holding. Three Class II<sup>116,121,125</sup> and 2 Class III studies<sup>134,138</sup> found that the combination of sucrose (with variable dosing including 2 mL of 12%, 0.5 mL of 24%, or 2 mL of 30%) plus nonnutritive sucking tended to be more effective than sucrose and/or a pacifier alone. In 1 Class III study in very-low-birth-weight, preterm infants, Stevens et al<sup>114</sup> did not find a difference between the sucrose plus pacifier group and the water plus pacifier group. Another Class III study found sucrose plus a pacifier to be more effective than water plus a pacifier in preterm infants during portions of the retinal examination of prematurity, considered a "highly invasive" procedure.<sup>137</sup>

Two Class II studies compared sucrose plus holding versus sucrose or holding alone during heel stick.<sup>120,131</sup> Both found that sucrose and sucrose plus holding reduced crying or facial

expressions of pain compared with controls. Reis et al<sup>144</sup> compared the combination of sucrose, nonnutritive sucking, and holding versus water in older infants and found a reduction in crying in the treatment group.

#### Safety of sucrose

Overall, adverse events appear to be uncommon and minor. Eight trials including more than 800 infants commented that no adverse effects of sucrose administration had been noted.<sup>108,114,124-126,138,139,144</sup> Only Gibbins et al<sup>116</sup> noted any adverse events: 3 episodes of desaturation in the treatment group receiving oral sucrose through a syringe, 2 episodes in the pacifier group, and none in the combined sucrose plus pacifier group. These events were too infrequent to perform statistical analysis. As reported in the Cochrane review, no intervention was required. One infant choked on the water and pacifier but recovered within 10 seconds.

A single, older study that was investigating the use of nutritional supplementation in very-low-birth-weight infants (<1.3 kg) administered frequent doses of calcium lactate in a 20% sucrose vehicle (with an osmolality of >1,700 mOsm/kg H<sub>2</sub>O), and found an increased risk of necrotizing enterocolitis.<sup>146</sup> This raised concerns about the use of sucrose in at-risk infants. Although most subsequent studies administering sucrose for analgesia have been designed to evaluate efficacy rather than safety, Stevens et al,<sup>114</sup> in a study of 122 very-low-birth-weight, preterm infants, did not report an increased risk of necrotizing enterocolitis with a pacifier containing 0.1 mL of 24% sucrose. Necrotizing enterocolitis is generally not a risk in the ED population.

#### 4. Is chloral hydrate effective and safe for providing procedural sedation in children in the ED?

*This critical question about chloral hydrate was included for completeness because of its use in some practice settings. A previous clinical policy focused on the efficacy and safety of etomidate, fentanyl/midazolam, ketamine, methohexital, pentobarbital, and propofol for achieving sedation and analgesia in pediatric patients undergoing procedures in the ED.<sup>12</sup> These recommendations about the safety and efficacy of chloral hydrate do not imply superiority to the above medications. See Appendix C for the recommendations from the previous clinical policy.*

#### Patient Management Recommendations for Chloral Hydrate

##### Level A recommendations.

- (1) Chloral hydrate may be used to provide effective procedural sedation in pediatric patients undergoing painless diagnostic studies. However, children receiving chloral hydrate should be properly monitored and managed by appropriately trained personnel due to the risk of respiratory depression and hypoxia.
- (2) Chloral hydrate should not be considered a first-line agent in children older than 48 months because of decreased efficacy as compared with younger children.

**Level B recommendations.** None specified.

**Level C recommendations.**

- (1) Chloral hydrate has the potential for re sedation and may produce residual effects up to 24 hours after administration.
- (2) Chloral hydrate may be used safely and effectively in properly monitored children who have congenital cardiac anomalies and are undergoing painless diagnostic procedures.
- (3) Chloral hydrate should not be used in children with neurodevelopmental disorders due to an increased incidence of adverse effects and decreased efficacy as compared with healthy children.
- (4) Pediatric patients receiving chloral hydrate should not be intentionally fasted because of increased procedural sedation failure rates.

The evidentiary basis for the efficacy and safety of a given drug may differ. Considering that significant adverse events are generally rare, it is likely that there is stronger evidence for efficacy than for safety. When assigning one overall recommendation for a given drug based on combining these 2 distinct attributes (efficacy and safety) of the drug, the lowest most conservative level of evidence has been designated.

**Efficacy of Chloral Hydrate**

Key words/phrases for literature searches: chloral hydrate, procedural sedation; age 1-18 years.

Chloral hydrate is a sedative hypnotic agent first introduced into clinical practice in the middle 1800s. The drug may be administered orally or rectally and has been described as an anxiolytic adjunct for dental procedures and as a single or combined sedative agent for painless diagnostic studies. The oral preparation is reported as having a bitter unpalatable taste that frequently requires administration in a flavored vehicle to disguise its taste. In 1 Class II study, 30% of children would not accept the chloral hydrate orally and required rectal administration, and 30% of the remaining 108 patients vomited immediately after oral administration of the drug, yet there were no complications or serious adverse effects and successful sedation occurred in 95% of the patients.<sup>147</sup>

The efficacy of chloral hydrate as a sedative for diagnostic or therapeutic procedures was 92% to 100% in 4 Class I studies,<sup>148-151</sup> 85% to 100% in 8 Class II studies,<sup>147,152-158</sup> and 80% to 100% in 12 Class III studies.<sup>49,159,160-169</sup>

Two studies were done in the ED: 1 Class I study with 100% effectiveness<sup>151</sup> and 1 Class III study with 88% effectiveness.<sup>167</sup> In other studies, chloral hydrate sedation was used for the performance of a diagnostic imaging study (computed tomography [CT] or magnetic resonance imaging [MRI] scan),<sup>149-156,158-160,162-165,168-171</sup> echocardiogram,<sup>147,148,157,166</sup> electroencephalogram (EEG),<sup>172</sup> hearing testing,<sup>49</sup> various procedures (CT, MRI, bone scan, EEG, other),<sup>160,168,173</sup> radiation therapy,<sup>161</sup> and dental procedures.<sup>174</sup>

The dose of chloral hydrate administered generally varied between 50 and 100 mg/kg, with most studies providing the option of administering additional doses if adequate clinical

effects were delayed. Two of the 3 Class I studies with greater than 92% efficacy used 75 mg/kg as their initial dose, with a third study using 70 mg/kg or 100 mg/kg.<sup>148,150,151</sup> In Class II studies with greater than 90% efficacy, dosages varied from 50 mg/kg to 100 mg/kg.<sup>147,153,154,156</sup>

Sedation failure rates are decreased when a second dose of chloral hydrate (up to a maximum of 2 g or 100 mg/kg, whichever is lowest) is given. First dose/second dose success rates for chloral hydrate are Class I 60%/93%,<sup>148</sup> 64%/92%,<sup>149</sup> Class III 89%/98%,<sup>170</sup> 88%/90%,<sup>160</sup> and 84.5%/94.5%.<sup>49</sup> Reports of success rates that listed just second doses included Class III 98%,<sup>159</sup> 99.3%,<sup>162</sup> 98.7%,<sup>163</sup> and 99.5%<sup>165</sup> (with hydroxyzine also given if age >1 year).<sup>165</sup>

Multiple doses of chloral hydrate were required to achieve high levels of efficacy in some studies. In the only Class I study designed to identify the optimal dose of chloral hydrate, 28% of children initially sedated with 70 mg/kg required supplemental chloral hydrate compared with 13% of children initially receiving 100 mg/kg.<sup>149</sup>

Adequate sedation occurred in 64% of patients receiving an initial dose of 70 mg/kg versus 87% for an initial 100 mg/kg dose. After subsequent dosing, 92% of children in the 70 mg/kg group and 100% of those in the 100 mg/kg group were successfully sedated. They developed the following formula to determine the optimal dose of chloral hydrate according to age and weight: Dose (mg/kg) = 56 + (0.8 × age in months).<sup>149</sup> In a Class II study, a lower dose yielded higher sedation failure rates, whereas higher doses increased the incidence of adverse reactions.<sup>153</sup>

In addition to the total dose of chloral hydrate administered, chloral hydrate's efficacy is affected by age, the patient population (special health care needs or not), and other factors. Failed sedations were noted to increase with increasing age.<sup>147,153,154,158,160,167,168,170,171,173</sup> In 2 Class II studies, failed sedations were most common in children older than 48 months.<sup>147,154</sup> The efficacy of chloral hydrate in a Class II study decreased with increasing age from 98% in children younger than 12 months to 74% in children 6 to 11 years of age.<sup>154</sup> Sedation failure rates were greater than 15% for age older than 7 years, less than 7.5% for age up to 7 years, and less than 5% for age younger than 3 years.<sup>153</sup> A Class III study found that chloral hydrate sedation was successful in 84% of children greater than or equal to 3 years of age versus 99% of children less than 3 years of age.<sup>166</sup> A Class III ED study found the following first dose/second dose success rates based on age: 0 to 0.9 years 98%/100%, age 1 to 1.9 years 84%/91%, 3 years 76%/85%.<sup>167</sup> In another Class III study, the sedation failure rate for children older than 4 years was higher (20% versus 12.5%) than for younger children.<sup>160</sup> A study of hospital-wide procedural sedation in children noted that those who had failed procedures with chloral hydrate were significantly older (3.6 years) than children who were successfully sedated (2.6 years).<sup>173</sup>

It is unclear from the literature whether these failures with increasing age are related to deficiencies with chloral hydrate or

whether older children who require sedation for diagnostic studies may be more likely to have neurodevelopmental problems that make their sedation more difficult.

Studies found a decreased efficacy of chloral hydrate sedation in certain patient populations. Chloral hydrate's success rate was only 80% in children with central nervous system disorders in a Class II study<sup>153</sup> and 73% in children with neurologic disorders (versus 4% for "normal" children) in a Class III study.<sup>160</sup>

Another article (Class III) found that "most failed" sedations with chloral hydrate occurred in "children with seizure disorders or retardation."<sup>168</sup> Failure to achieve adequate sedation occurred in 71% of patients with a genetic disorder (Class II study).<sup>147</sup> Olson et al<sup>172</sup> found that only 9% of sedations with chloral hydrate for EEGs were unsuccessful but that 65.9% of those who could not be adequately sedated had a history of developmental delay or autism. In contrast to patients with neurodevelopmental disorders or genetic syndromes, children with congenital heart disease, including those with cyanotic heart disease, do not have a higher sedation failure rate or increased adverse effects with chloral hydrate.<sup>147,148,157,166</sup>

There are other factors that may affect chloral hydrate's efficacy. One Class III study<sup>49</sup> and 1 Class II study<sup>157</sup> demonstrated that the fasting state of a child affected the dose of chloral hydrate, with fed children demonstrating a quicker onset and a lower dose than fasted children. The greater dose requirement in fasted children was thought to be related to the longer duration to onset, which also resulted in a longer duration of action.<sup>49,157</sup> In one Class II study, the efficacy of chloral hydrate was increased when timed to coincide with nap times.<sup>157</sup>

In direct comparison studies, chloral hydrate demonstrated comparable or superior efficacy to oral midazolam and pentobarbital.<sup>148,150,151,155,156,158,162-164,174</sup>

### Safety of Chloral Hydrate

Key words/phrases for literature searches: chloral hydrate, procedural sedation; age 1-18 years.

Three Class I studies demonstrated the presence of side effects such as vomiting (9% to 18%) and paradoxical excitement (0% to 2%) in children sedated with chloral hydrate, but no cardiac or respiratory adverse effects were reported.<sup>149-151</sup>

In 5 Class II studies the following was reported: vomiting 2% to 30%, paradoxical excitement 1% to 6%, and desaturation 0% to 4%.<sup>147,153,154,156,158</sup> In 4 Class III studies, vomiting occurred in 0% to 2%, paradoxical excitement in 0% to 15%, prolonged sedation in 0% to 1%, and desaturation in 0% to 7.6%.<sup>162,163,165,169</sup> In all instances the hypoxia was responsive to positional maneuvers or supplemental oxygen.

In a single study of 7 neonates with pulmonary hypertension or persistent fetal circulation, desaturation occurred in 57%; treatment with additional oxygen was used in some infants but none required BVM support or intubation.<sup>155</sup>

In 3 studies of children undergoing echocardiograms, no adverse effects were noted in one study,<sup>148</sup> whereas another

study did demonstrate a 5% decrease in saturation in 6% of patients, which was more prominent in children with genetic disorders.<sup>166</sup> A Class II study demonstrated no difference in cyanotic and acyanotic children sedated with chloral hydrate.<sup>147</sup>

Three studies reported clinical effects the day after sedation.<sup>157,170,175</sup> One Class II study noted grogginess and irritability in children younger than 6 months of age, and grogginess, irritability, and motor instability in children 6 months to 2 years of age.<sup>157</sup> One Class III study reported unsteadiness in 68% and hyperactivity in 29% of sedated children the day after treatment.<sup>170</sup> A second Class III study comparing chloral hydrate and midazolam noted motor imbalance in 31% of children receiving chloral hydrate compared with 18% of the midazolam group ( $P < 0.05$ ).<sup>175</sup> In the same study, agitation was noted in 18% of the chloral hydrate group compared with 8% of the midazolam group ( $P = \text{NS}$ ). For both the chloral hydrate and midazolam groups, only 48% returned to baseline activity within 8 hours, although 89% were at baseline at 24 hours.<sup>157,170,175</sup>

A single Class I study demonstrated the occurrence of vomiting, excitement, and nausea in 21% of children sedated with 2 different doses of chloral hydrate, 70 mg/kg or 100 mg/kg.<sup>149</sup> There was no difference in incidence of these effects between the 2 dosage groups.

One Class III study did demonstrate that chloral hydrate patients were more likely to achieve an unintended deeper level of sedation than occurred with other sedation agents.<sup>43</sup> However, this study provided no data on the specific dosing, personnel, or circumstances of the chloral hydrate use and did not report any need for rescue intubation or permanent neurologic deficits in these children.<sup>43</sup> In another anecdotal study, 13 deaths or severe neurologic injuries were found after chloral hydrate administration.<sup>176</sup> None of these severe adverse events occurred in the ED setting. The cases were identified in a review of US Food and Drug Administration records or surveys of specialists, with no information reported on monitoring or qualifications of personnel performing the procedures. Five of these patients were dental patients; 5 were undergoing radiologic procedures; 2 were cardiology procedures; and 1, an audiology procedure. In the 7 cases in which chloral hydrate was the single agent administered, 4 patients received an overdose. Significant preexisting medical problems were noted in 8 of the 13 patients. No information on the total number of cases sedated was presented.<sup>176</sup> This one report<sup>176</sup> is in contrast to the many formal Class I, II, and III studies involving chloral hydrate that demonstrated no significant adverse events and in particular no deaths or severe neurologic injuries.

Two studies found significant decreases in the oxygen saturation occurring with chloral hydrate in half of patients with genetic disorders: 50% of patients with Down's syndrome in the Class II Coskun et al<sup>147</sup> study and 54% in the Class III Napoli et al<sup>166</sup> study.

In contrast to patients with genetic syndromes or neurologic

disorders, children with congenital heart disease, including those with cyanotic heart disease, are not at particular risk with chloral hydrate sedation.<sup>175</sup>

One particular concern with chloral hydrate is its potential for re-sedation because of its long half-life. Cote et al<sup>176</sup> and Malviya et al<sup>175</sup> note the possibility of re-sedation, in which the infant or child appears to have recovered and meets discharge criteria but then is re-sedated because of circulating active metabolites and residual drug.

Furthermore, the response to chloral hydrate's sedative effects in a given patient may be varied and unpredictable. In a telephone follow-up of 376 children who received sedation for diagnostic radiology studies, 89% received chloral hydrate and 11% received midazolam as the primary sedative. After discharge, medical advice was sought for 15 children (4%). Three children required a visit to the ED for prolonged or excessive sedation. All of these children had received a recommended dose of chloral hydrate (61 mg/kg to 77 mg/kg) as a sole sedative. In one child, the procedure had been aborted because of inadequate sedation in the hospital, yet the child became difficult to arouse at home.<sup>175</sup>

A study of procedural sedation in a pediatric ED at a children's hospital used chloral hydrate in 122 patients (10% of their procedural sedation regimens) and reported no adverse events with chloral hydrate and no serious complications in their 1,180 patients.<sup>177</sup> A hospital-wide study of 1,140 children undergoing procedural sedation also revealed no long-term sequelae.<sup>173</sup>

The use of chloral hydrate has been controversial, with some critics of the opinion that it should be banned.<sup>178,179</sup> Serious complications<sup>180-185</sup> and deaths<sup>32,176,186-189</sup> have been associated with chloral hydrate. Like other sedative hypnotic agents, chloral hydrate has the potential for central nervous system depression, suppression of respiratory activity, direct or hypoxia-induced arrhythmias, and airway obstruction secondary to skeletal muscle relaxation. However, many of the adverse patient outcomes reported with chloral hydrate occurred in reports in which proper patient monitoring or clinician competence was not documented. In all graded studies included in this analysis, chloral hydrate did not demonstrate any of the catastrophic patient outcomes found above. Proper patient monitoring and improved physician training may account for the improved results in the more recent studies of chloral hydrate use.

## 5. What clinical indicators support safe discharge after pediatric procedural sedation in the ED?

### Patient Management Recommendations

**Level A recommendations.** None specified.

**Level B recommendations.** None specified.

**Level C recommendations.** No universally applicable, evidence-based set of clinical indicators has been established. Emergency physicians, in conjunction with their institutions, should develop criteria for safe discharge.

Key words/phrases for literature searches: discharge, procedural sedation; age 1-18 years.

Most children who have undergone procedural sedation in the ED are discharged home. Determining discharge readiness is a process that takes place in each of these discharged cases. The intent of this process is to ensure that a child will not experience serious or life-threatening adverse events at home, where immediate medical intervention is not available. The balance between safety and practicality results in a tension between prolonged observation and premature discharge. The ideal solution would be a universally applicable, evidence-based set of clinical criteria that, if met, would ensure safe discharge from the ED at the earliest possible time. Unfortunately, we have yet to identify such a set of criteria.

Recommended criteria have been published by a number of organizations, such as the ASA,<sup>22</sup> the AAP,<sup>24</sup> the Canadian Association of Emergency Physicians,<sup>1</sup> and the Australasian College for Emergency Medicine.<sup>190</sup> None of these are evidence based. Comprehensive review of the literature evaluating clinical indicators/discharge criteria has failed to yield well-supported measures of discharge readiness after pediatric procedural sedation.<sup>170,176,187,191-200</sup>

We identified 2 studies directly addressing pediatric-specific criteria for postsedation discharge readiness from an outpatient setting. The first is a Class III study of 29 children who underwent echocardiography facilitated by chloral hydrate (n=27) or midazolam/diphenhydramine (n=2) sedation given orally.<sup>197</sup> All children were ASA physical status classification III due to congenital cardiac diseases. These authors used Bispectral Index monitoring and 2 clinical scoring systems: the University of Michigan Sedation Scale<sup>201</sup> and a modified Maintenance of Wakefulness Test.<sup>202</sup> The authors concluded that incorporating these 2 clinical scoring systems into discharge decisionmaking prolonged the observation time (from a mean of 16 minutes to a mean of 75 minutes) but resulted in discharged children having Bispectral Index scores closer to baseline measurements than when traditional criteria were used. There are several problems with the applicability of this study to the ED. The population studied was medically complicated and likely to be dissimilar to most children in most EDs. The children underwent a relatively painless procedure, whereas many procedures in the ED are painful and require higher doses of sedation agents, which can complicate discharge readiness. Bispectral Index scoring has not been adequately validated as a surrogate marker for discharge readiness, nor has it been shown to be more useful than clinical observation.<sup>203</sup> Bispectral Index monitoring is not applicable in cases involving ketamine sedation.<sup>204</sup> The modified Maintenance of Wakefulness Test proposed by the authors requires a 20-minute period in a "soporific environment (ie, dim, quiet room)," an environment unlikely to be present in many EDs.

In the other Class III study, Newman et al<sup>205</sup> found there were no serious adverse events beyond 25 minutes after the final medication administration if a serious adverse event did not

occur within the first 25 minutes. However, the heterogeneity of this study population, the different sedative agents used, and the various routes of administration make universal time-based recommendations difficult.

It is likely that discharge decisionmaking will remain a complex process. The factors likely to influence this decision include the pharmacologic properties of the sedation agent or agents chosen, the route of administration, the procedure performed, preexisting medical conditions or ASA physical status classification, the use of reversal agents, the occurrence of adverse events during the procedure, individual patient factors (eg, age, metabolism, polypharmacy, obesity), and the social circumstances of the child. Further study may yield generally applicable clinical discharge criteria. Professional organization consensus guidelines have been developed to assess discharge readiness and may be used to develop institutional protocols or guidelines.

This clinical policy may also be found at:

<http://www.acep.org>

<http://www.jenonline.org> (June 2008)

<http://www.pedsnurses.org/> and

As a link at <http://www.capsa.org/>

When this document is cited, the following citation format is suggested: Mace SE, Brown LA, Francis L, Godwin SA, Hahn SA, Howard PK, Kennedy RM, Mooney DP, Sacchetti AD, Wears RL, Clark RM. EMSC Panel on Critical Issues in the Sedation of Pediatric Patients in the Emergency Department. Clinical policy: critical issues in the sedation of pediatric patients in the emergency department. *Ann Emerg Med.* 2008; 51:378-399, e1-e57.

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**Appendix A.** Literature classification schema.\*

<b>Design/Class</b>	<b>Therapy<sup>†</sup></b>	<b>Diagnosis<sup>‡</sup></b>	<b>Prognosis<sup>§</sup></b>
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.

<sup>†</sup>Objective is to measure therapeutic efficacy comparing  $\geq 2$  interventions.

<sup>‡</sup>Objective is to determine the sensitivity and specificity of diagnostic tests.

<sup>§</sup>Objective is to predict outcome including mortality and morbidity.

**Appendix B.** Approach to downgrading strength of evidence.

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

**Appendix C.** Recommendations from the 2004 clinical policy.<sup>12</sup>

- I. Is etomidate effective for providing procedural sedation in children in the ED?**  
*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?**  
*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.
- III. Are fentanyl and midazolam effective for providing procedural sedation in children in the ED?**  
*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?**  
*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.
- V. Is ketamine effective for providing procedural sedation in children in the ED?**  
*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?**  
*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?**  
*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.
- VIII. Is methohexital effective for providing procedural sedation in children in the ED?**  
*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?**  
*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.
- X. Is pentobarbital effective for providing procedural sedation in children in the ED?**  
*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?**  
*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.
- XII. Is propofol effective for providing procedural sedation in children in the ED?**  
*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.

**Appendix C (continued).****XIII. Is propofol safe for providing procedural sedation in children in the ED?**

*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.

Evidentiary Table.

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Agrawal et al <sup>26</sup>	2003	Prospective, observational study	Consecutive patients requiring procedural sedation during 11 mo; 905/1,014 patients had adequate fasting documentation; age 5 days to 31 y, median age 5.4 y; 580 (57%) male; no gastric emptying agents or anti-emetic medications were documented although patients receiving medications for intractable vomiting were excluded	Observational protocol to detect adverse events including desaturation, prolonged sedation, airway complications, emesis, and aspiration	ASA physical status class I: 785 (77%), class II: 188 (19%), class III: 41 (4%), no class IV or V, 56% of patients not fasted; no difference in adverse events between fasted and unfasted groups; 77 adverse events occurred in 68/1,014 patients (6.7%; 95% CI 5.2% to 8.4%); all adverse events were minor and successfully treated; adverse events occurred in 32/396 (8.1%) patients who met and 35/509 (6.9%) patients who did not meet fasting guidelines; median fasting duration for patients with emesis was 6.8 h for solids and 5.8 h for clear liquids; emesis occurred in 15 (1.5%) patients; 11/15 patients with emesis were sedated with ketamine; median age for emesis 11.1 y vs 5.3 y for patients without emesis; odds ratio for emesis with ketamine was 3.2 ( $P=.04$ ); there were no episodes of aspiration	Inadequate power to determine differences in aspiration after emesis; nonblinded sedation recorders (ED nurses caring for patients); no follow-up of patients after ED discharge although patients had to be deemed back to normal before discharge from the ED; no data on why physicians waited or did not wait; could be physicians self selected (bias)	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Green and Krauss <sup>30</sup>	2002	Review	Review of pulmonary aspiration risk during ED procedural sedation			Design; risk of aspiration during ED procedural sedation appears to be extremely low; there is no compelling evidence that mandates specific times for pre-sedation fasting for solids or liquids	III
Babl et al <sup>35</sup>	2005	Prospective observational study	Incidence of adverse events with preprocedural fasting for nitrous oxide procedural sedation in the ED; 220 children underwent painful procedures; 82% got 70% nitrous oxide; 18% got 50% nitrous oxide; 12% also got morphine; ages 14 mo to 17 y; median age 8 y 3 mo, 60% boys; 209 (95%) patients were ASA class I or II, 11 (5%) were class III, no class IV or V; authors performed follow-up calls with 207 patient families to document any late sequelae; no gastric emptying agents or anti-emetic medications were documented	Prospectively documented adverse outcomes defined as minor and serious; serious affects included but were not limited to airway compromise, desaturation, and aspiration	Fasting status documented in 218 patients (99.1%); orthopedic procedures 45%, lacerations 21%, vascular access 18%; 86% moderate, 7% deep, 7% poorly sedated; ASA guidelines met for solids in 29%, clear liquids in 79%; 46 minor events occurred in 37 patients (17%); no aspiration; emesis in 6% meeting and 7% not meeting fasting guidelines for solids; no correlation between fasting status and vomiting; no major adverse events; 5% of patients in follow-up calls admitted to vomiting after returning home	71% of patients undergoing ED procedural sedation did not meet fasting guidelines; no association between preprocedural fasting and emesis; no serious adverse events; 60 patients missed in chart review but found no difference from study subjects; inadequate power to determine differences in aspiration after emesis; no data on physicians as to why they waited or did not wait, could be physicians self selected (bias)	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Egelhoff et al <sup>36</sup>	1997	Retrospective cohort	6,006 pediatric outpatients of a radiology department; ages 1 mo to 18 y; retrospective review for safety and efficacy with the sedation during the imaging study; fasting guidelines: 3 h for liquids and solids in children <1 y and 8 h with no solids and 4 h with no liquids for children 12 mo and older; milk was a solid; the 3 drugs used were chloral hydrate, pentobarbital, and fentanyl; no gastric emptying agents or anti-emetic medications documented	Sedation complications, and rate of successful sedation	65% of patients received pentobarbital with 38% receiving fentanyl as well; 35% received chloral hydrate; 4 required overnight hospitalization because of CNS depression with no sequelae; no cardiovascular or respiratory arrest occurred; 48 patients experienced transient respiratory depression; 63% (N=3,783) were contacted for follow-up; delayed complications in 29 (0.77%) children, with excessive vomiting in 20 (0.53%) patients and no hospitalizations; sedation failure was about 1%	Design of study the largest limitation; not designed to specifically evaluate fasting guidelines	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Roback et al <sup>17</sup>	2004	Retrospective review of prospective database	2,497 patients received procedural sedation and analgesia; 412 patients were excluded for receiving oral or intranasal drugs (n=95) or for bronchoscopy by nonemergency physicians (n=317); a total of 2,085 patients received parenteral sedation by emergency physicians; ages: 19 days to 32.1 y (median age 6.7 y); fasting time documented in 1,555 (74.6%) patients, 60.2% of these male; median fasting time before sedation was 5.1 h (range 5 min to 32.5 h); various medications used including ketamine, ketamine/midazolam, midazolam, fentanyl/midazolam, and morphine/midazolam; no gastric emptying agents or anti-emetic medications documented; comparisons were made on the incidence of adverse events according to length of preprocedural fasting; all unmedicated patients included; all patients taking known gastric motility agents excluded; ASA physical status not documented	Incidence of vomiting, aspiration, or respiratory events	No aspiration episodes; incidence of adverse events not related to NPO time; 150 patients fasted <2 h; 391 patients fasted 2-4 h; adverse events included desaturations (169 [8.1%]), apnea vomiting (156 [7.5%]), and (16 [0.8%]); and laryngospasm (3 [0.1%]); 1,096/2,085 sedations for fracture or dislocation reduction, 411 patients for laceration repair, and 95 patients for radiologic procedures; others were mixture of predominantly painful procedures	Retrospective review of prospectively collected data; fasting time documented in only ¼ of patients; brings into question the validity of the results; type of ingestion of last meal (liquid, solid) not documented; documentations may not have detected key information as nursing may not have been as thorough because it was for a data base and not a study initially; variety of medications and doses; adequacy of sedation not noted; other medical conditions?	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Kennedy et al <sup>38</sup>	1998	Prospective, single-blinded, randomized, controlled trial	260 patients; age 5–15 y requiring orthopedic procedures in ED; ASA status I–II; videotaped blinded assessment of sedation events; compared ketamine/midazolam versus fentanyl/midazolam; dosing regimens: midazolam 0.1 mg/kg, maximum 2.5 mg every 3 min until sedated; fentanyl 0.5 mg/kg every 3 min until decrease response to verbal/painful stimuli versus ketamine 0.5 mg/kg every 3 min (up to 2 mg/kg)+glycopyrrolate 5 mg/kg up to 250 mg	Recorded data included time of last meal and 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	Safety: mean time to last oral intake and sedation for subjects who vomited was 4.4 +/- 2.5 h, compared with 5.0 +/- 2.4 h who did not; no aspirations documented; ketamine/midazolam had more vomiting in 7-day period after procedure (4% versus 0%) ( $P=.03$ ); hypoxia in 6% of ketamine/midazolam group versus 25% in the fentanyl/midazolam group ( $P=.001$ ); breathing cues needed 1% for ketamine/midazolam versus 12% in fentanyl/midazolam ( $P=.001$ ), and oxygen required in 10% ketamine/midazolam versus 20% fentanyl/midazolam ( $P=.04$ ); 2 patients in ketamine/midazolam group required assisted mask ventilation versus 0 patients in fentanyl/midazolam group; efficacy: ketamine/midazolam had better efficacy measured by lower distress scores during procedure and increased orthopedic physician satisfaction; OSBD-R for ketamine/midazolam was lower than with fentanyl/midazolam $1.08\pm 1.12$ vs $2.70\pm 2.16$ ( $P<.0001$ )	Well-done randomized controlled trial not specifically designed to identify issues associated with preprocedural fasting such as solids versus liquids and their specific times of ingestion; only orthopedic procedures; results may not apply to younger patients; single-blind study; 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 after sedation slightly more common with ketamine/midazolam (4% versus 0%)	III

**Evidentiary Table (continued).**

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Basset et al <sup>42</sup>	2003	Prospective observational cohort	Consecutive case series of 393 propofol sedations for painful orthopedic procedures in tertiary care pediatric hospital ED; one patient with an ocular burn also included; opioid premed administered 1 min before propofol delivery; sedation forms; no gastric emptying agents or anti-emetic medications documented	Vital signs, need for airway assistance, fasting time, procedure time, sedation time	ASA classifications: 379 (96%) patients ASA I; 13 (4%) patients ASA II; 50 (13%) patients with fasting protocol violations with shortened fasting times were identified; 31 (8%) were fasted for less than 3 h for liquids; adverse events included: 1 episode of postsedation emesis, decrease in blood pressure in 331 (84%) children, 23 (6%) with bradycardia, 3 (0.8%) patients required brief bag-valve-mask; no patient required endotracheal intubation; no clinically significant aspirations	Depth of sedation not objectively observed; fasting was not the focus of the study although study violations were documented; no comparison group and no clear differentiation of NPO; only 13% with fasting period <3 h; otherwise 3 h cutoff within guidelines for clear liquids; does not delineate solids versus liquids in final numbers	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Hoffman et al <sup>43</sup>	2002	Retrospective cohort	960 prospectively coded sedation records; NPO criteria not met in 309/960 (32%) patients; in 45 of these (15%), NPO status not documented; ASA physical status: 501 patients ASA I, 353 patients ASA II, 56 patients ASA III, 14 patients ASA IV, and 2 patients ASA V; ASA status I or II in 89% of patients; age <2 y in 508 (53%)	NPO status and drugs used; type 1 complications included sedation failure; type 2 complications included all others such as respiratory and hemodynamic instability	Fasting question: deep sedation in 215 (22%) with only 65 (7%) documented planned deep sedation; adherence to NPO guidelines did not affect overall risk of complications 11/309 (3.6%) versus 29/651 (4.5%), and did not decrease the risk of type 2 complications 9/309 (2.9%) versus 18/651 (2.8%); complication risk was insignificantly different in patients without documented NPO status 3/45 (6.7%) vs 37/915 (4.0%); sedation failure was significantly higher in patients who met NPO criteria 20/921 (2.2%) vs 2/443 (0.5%); sedation failure was equal in targeted conscious and targeted deep sedation; 2 aspiration events occurred in patients who met NPO criteria and were deeply sedated with opioid-barbiturate combinations, 1 for radiologic procedure, the other for bronchoscopy; both patients required postprocedure care with overnight oxygen administration; aspiration incidence was 3.1% of patients who were deeply sedated or 0.21% overall	Fasting question: according to the authors the effect of NPO status on sedation outcome could not be adequately assessed in this study because inadequate NPO time was identified a priori as a risk factor, which should have altered the sedation plan; alternatively, sedation of infants and young children may be more difficult when they are hungry  Chloral hydrate question: no individual analysis of chloral hydrate cases to adjust for procedures, ages, or types of cases; no specification of severity of adverse events; no dosages, no ASA status; retrospective review of quality improvement records; no fixed procedure	Fasting II  Chloral Hydrate  Efficacy N/A  Safety III
<p>Chloral hydrate question: complication rate 3.8% in chloral hydrate group; chloral hydrate more likely to develop inadvertent deep sedation (OR 11.6; <math>P&lt;0.001</math>) or adverse event (OR 2.1; <math>P&lt;0.05</math>) overall</p>							

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Maekawa et al <sup>44</sup>	1993	Prospective, randomized, nonblinded	105 healthy children ages 1-14 y undergoing elective surgery broken into 3 NPO time periods: 2, 4, and 12 hours; prior the children were given set volume of apple juice; all ASA I physical status; gender was not documented; gastric aspirates taken through an orogastric tube from patients immediately after intubation; all patients were unmedicated; all patients taking known gastric motility agents were excluded	Gastric volume, serum glucose, ketones, triglycerides, NEFA, and cortisol levels	No difference in gastric fluid volume or pH and glucose level; fewer ketone bodies and NEFA in 2 h NPO patients	Apple juice, not other clear fluids	I
Splinter and Schaefer <sup>45</sup>	1990	Prospective, randomized, single blinded	122 healthy children ages 2-12 y undergoing elective operation were either NPO from midnight or allowed clear liquids up to 3 h preoperatively; no difference in gender or ASA status (exact numbers not reported); stomach contents aspirated by gastric tube following intubation	Gastric fluid volume and pH	No difference between the 2 groups' gastric fluid volume or pH	Does not evaluate NPO less than 3 h; both solid and liquid ingestion within current AAP/ASA guidelines	I
Ingebo et al <sup>46</sup>	1997	Prospective observational	Prospective observational study of 285 pediatric patients ages 1 to 18.6 y; gastric contents were collected by endoscopic suction immediately after intravenous sedation; duration of fasting after clear fluid ingestion ranged from .5 to 24 h, mean of 6.7±5.3 h; 49 patients fasted exactly 2 h, 3 patients fasted less than 2 h; patients were on a variety of unnamed medications, some used to treat gastric reflux; patients were instructed to not take any medications once milk and solids were discontinued	Gastric volume and pH	No difference in gastric volume or pH was found with different NPO times	Compared data to historical standards; does not specifically look at time from ingestion of milk and solids prior to sedation; only 3 patients fasted less than 2 h; broad patient ages; potential for increased gastric emptying effect from unnamed patient medications	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Soreide et al <sup>47</sup>	1996	Prospective, observational experiment	8 healthy female adults (median age 37 y) ate a light meal and underwent gastric ultrasounds at timed intervals to determine the presence of solids, and then a nasogastric placement to check for fluid volume; a gastric emptying study with paracetamol was performed	Presence of solids; nasogastric fluid volume; serum paracetamol concentration; gastric antral area	It took 240 min for all patients to be solids free; antral area returned to normal and paracetamol level peaked before all solids were gone	Adult women; only 8 subjects	II
Ghaffer et al <sup>48</sup>	2002	Retrospective observational	Pediatric patients receiving echocardiograms were retrospectively analyzed; 334 patients under the age of 3 y were divided into 2 groups and treated with chloral hydrate 80 mg/kg; group 1 (140 patients) had fasting times <2 h (average 80 min), whereas group 2 (184 patients) had fasting times more than 2 h (average 225 min); a subgroup of children <6 mo of age was analyzed; no gastric emptying agents or anti-emetic medications were documented although 10% of patients were given diphenhydramine (1 mg/kg)	Adequacy of sedation, minor and major complication rate	Increase (NS) in inadequate sedation in longer NPO group; patients <6 mo with longer fasting times had decreased efficacy compared with shorter fasting times ( $P=.03$ ); no major complications in either group; overall 9% minor complication rate; no difference in minor complications between the 2 groups	Retrospective design; chloral hydrate used as sedative; echocardiograms are not painful, may be inadequate for ED procedures; no follow-up on patients after treatment	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Keidan et al <sup>49</sup>	2004	Retrospective cohort	200 infants ages 1 to 26 mo undergoing hearing tests with chloral hydrate (50-60 mg/kg with option for additional 25 mg/kg if needed) sedation at one of 2 hospitals; one hospital's protocol adhered to fasting guidelines and one hospital followed no fasting guidelines; patients were redosed as needed; ASA physical status and gender were not identified; no gastric emptying agents or anti-emetic medications documented	NPO time, dose required, need for redosing, sedation time; efficacy determined by completion of study	Average fasting period was significantly longer in fasted patients than in nonfasted patients (5.7 vs 2 h; $P<0.001$ ); fasted patients had significantly higher sedation failure rate with the first dose of chloral hydrate compared with nonfasted patients (21% vs 11%; $P=0.03$ ), needed higher doses (83 mg/kg vs 61 mg/kg; $P<0.01$ ), were sedated for longer periods (103 min vs 73 min; $P<0.001$ ), and were discharged later; no significant difference in adverse events	Limited to chloral hydrate; may not be generalizable to painful procedures, no standardized data collection form; no follow-up attempts, child could have vomited after leaving hospital; sample size too small to detect aspiration; chloral hydrate was less effective in children with longer NPO time who needed more redosing and experienced more prolonged sedation	Fasting III Chloral hydrate Efficacy III Safety III
Litman et al <sup>55</sup>	1996	Nonrandomized trial; 20 patients, 11 boys, 9 girls; fasted children ages 1-3 y; no ASA listed; elective outpatient surgery	Premedicated with oral midazolam 0.5 mg/kg; given 15%, 30%, 45%, then 60% N <sub>2</sub> O for 4 min each	Levels of sedation (response to standard non-noxious stimuli); changes in respiratory rate, ET <sub>CO</sub> <sub>2</sub> , oxygen saturation, upper airway obstruction, respiratory impedance plethysmography	Sedation proportional to concentration of N <sub>2</sub> O; sedation scores significantly higher at 60% N <sub>2</sub> O than all other N <sub>2</sub> O concentrations ( $P<0.02$ ); at 60% N <sub>2</sub> O 1/3 patients each not sedated, conscious sedation, or deep sedation; 1 unresponsive to intravenous insertion; no change in respiratory rate, ET <sub>CO</sub> <sub>2</sub> , or oxygen saturations with increasing concentration N <sub>2</sub> O; 1 had emesis; no hypoxemia	Study in operating room; short time at each concentration may be too short to see cumulative effects; no painful stimulation; small number	Efficacy II Safety II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Litman et al <sup>56</sup>	1997	Nonrandomized trial; 34 patients, mean age 3.8 y, 19 boys; healthy, fasted children, restorative dental surgery under general anesthesia; age range 1-9 y	Oral midazolam 0.7 mg/kg then 40% N <sub>2</sub> O (mixed with <30% oxygen) for 15 min; excluded patients with conditions that might increase upper respiratory obstruction, eg, enlarged tonsils	Levels of sedation (response to standard stimuli); changes in respiratory rate, ETCO <sub>2</sub> , oxygen saturation, upper airway obstruction, respiratory impedance plethysmography	All oxygen saturations >92%, no significant upper airway obstruction; ETCO <sub>2</sub> ↑ to >45 in 4 patients after N <sub>2</sub> O begun (hypoventilation); overall, no clinically significant difference in oxygen saturations/ETCO <sub>2</sub> /VT, or V <sub>T</sub> /T <sub>I</sub> ; sedation levels for midazolam alone (before N <sub>2</sub> O given) vs midazolam plus N <sub>2</sub> O were: unседated 14 vs 12, conscious sedation 19 vs 17, deep sedation 1 vs 3, general anesthesia 0 vs 1	Study in operating room; no painful stimulation, small sample size; patients with upper airway abnormalities excluded	Efficacy II Safety II
Litman et al <sup>57</sup>	1998	Nonrandomized trial; 32 patients; mean age 3.9 y; age range 1-9 y; fasted; ASA I/II; 16 males, 16 females; outpatient dental procedures	Premedicated with 70 mg/kg oral chloral hydrate; 1 h later, began 30% then 50% N <sub>2</sub> O using anesthesia circuit that limited FiO <sub>2</sub> to ≤30%	Levels of sedation (response to standard stimuli); changes in respiratory rate, ETCO <sub>2</sub> , oxygen saturation, upper airway obstruction, respiratory impedance plethysmography	No oxygen saturation <92%; ETCO <sub>2</sub> >45 in 77% on room air with chloral hydrate alone, 94% on 30%+chloral hydrate ( <i>P</i> =0.007), 97% on 50%+chloral hydrate ( <i>P</i> =0.02); 4 had partial upper airway obstruction with 30%; after chloral hydrate alone: 25% not sedated, 31% conscious sedation, 44% deep sedation; after 30% N <sub>2</sub> O, 6% not sedated, 94% conscious sedation; after 50% N <sub>2</sub> O, 3% not sedated, 94% conscious sedation, 3% general anesthesia (1 patient)	Study in operating room; patient administered ≤30% oxygen with the N <sub>2</sub> O, ie, N <sub>2</sub> O not blended with oxygen; fasted children; small sample size	Efficacy II Safety II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Averley et al <sup>64</sup>	2004	Prospective, blinded, randomized, controlled trial; anxious patients, ages 6-14 y, in dental clinic, sedated by anesthesiologists; 697 healthy children, ASA I/II, mean age 9.5 y; 44.6% male (311/697) 55.4% females (386/697)	Intravenous midazolam to effect with air, 40% N <sub>2</sub> O, or 40% N <sub>2</sub> O plus sevoflurane	Primary outcome successful completion of dental procedure with child responsive to verbal commands; Wong-Baker scale by patient; standard behavioral and sedation scales by dentist; standard vital signs, ETCO <sub>2</sub> /N <sub>2</sub> O, capnography, oxygen saturation	40% N <sub>2</sub> O no better than air ( $P=0.07$ ); successful completion of dental procedure in 54% with air, 80% with N <sub>2</sub> O, and 93% with N <sub>2</sub> O plus sevoflurane; N <sub>2</sub> O significantly improved behavior during IV starts; all were responsive; no significant adverse events; 6 vomited	Dental procedures; randomization to air stopped midtrial; may have weakened comparison of N <sub>2</sub> O to air	Efficacy II Safety III
Berge <sup>65</sup>	1999	Nonrandomized trial; anxious children and adults for elective oral surgical procedures in dental suite; 241 sedations in 194 patients, 48% males, 183 ASA I, 11 ASA II, mean age 14.5 y (3-46 y), 77% <19 y; median N <sub>2</sub> O concentration 50%	Maximum of 65% N <sub>2</sub> O administered by oral surgeon for dental/oral surgical procedures; local anesthetic used	Standard assessment tool for anxiety of patient; primary outcome: procedure completed without problems per oral surgeon; standard vital signs monitored, oxygen saturation	One emesis; no major adverse events; ASA II and very anxious patients more likely unsuccessful; N <sub>2</sub> O effective adjunct to local anesthesia; 8.2% minor adverse effects, easily treated	Dental study; subjective outcome measure; about one-fourth patients were adults	Efficacy III Safety II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Houpt et al <sup>66</sup>	1996	Blinded, randomized, crossover trial in healthy anxious children; 24 patients, mean age 32 mo, for dental procedures; all patients restrained, fasted >4 h; no ASA or gender listed	Oral diazepam 0.5 mg/kg then either 50% N <sub>2</sub> O for 20 min followed by 100% oxygen or 100% oxygen for 20 min then 50% N <sub>2</sub> O	Standardized sedation scale by chair-side observers and from videotapes; successful sedation ("enabled ability to carry out procedure"); vital signs, oxygen saturation	Groups similar for sleepiness, movement, crying; with 50% N <sub>2</sub> O, 71% of patients very good or excellent vs 31% with 100% oxygen; successful sedation (lack of crying or movement that interrupted treatment) in 83%; overall sedation with N <sub>2</sub> O better 56% of time, same 31%, worse 13%	Dental study; patients restrained	Efficacy II  Safety II
Houpt et al <sup>67</sup>	2004	Nonrandomized trial; healthy children requiring dental restoration in dental clinic; 59 patients, mean age 7.7 y, (age range 4-13 y); 36 males, 23 females, no ASA listed	50% N <sub>2</sub> O for 5 min before dental procedures in healthy children	Observations after 5 min 50% N <sub>2</sub> O: behavior (Frankel scale), psychomotor effects (Bender Visual Motor Gestalt Test), and perceptions of 50% N <sub>2</sub> O effects	With N <sub>2</sub> O, "90% relaxed behavior," 95% liked effects, 70% felt good, 2% felt bad, 86% felt different; no difference by age/previous experience; no significant difference in increased errors with psychomotor test between age groups	Dental study; small significant effect on psychomotor ability, uncertain of clinical importance	Efficacy III  Safety N/A
McCann et al <sup>68</sup>	1996	Placebo-controlled, double blinded, randomized, controlled trial; crossover comparison for dental procedures, 40 visits, mean age 45 mo (age range=36-60 mo); ASA, gender not given	50% N <sub>2</sub> O or 100% oxygen in anxious children, sedated with 40 mg/kg chloral hydrate and 2 mg/kg hydroxyzine	Standard behavior scales (OSUBRS); vital signs, oxygen saturation and ET <sub>CO</sub> <sub>2</sub>	No significant physiologic or behavioral differences between N <sub>2</sub> O and oxygen (when co-administered with chloral hydrate/hydroxy); trends of less increase in heart rate during anesthesia injection; greater increase in ET <sub>CO</sub> <sub>2</sub> , lower behavioral scores under N <sub>2</sub> O; significant variability in responsiveness to N <sub>2</sub> O	Dental study; pretreatment with sedatives unable to analyze effect of N <sub>2</sub> O alone; small number patients (N=20)	Efficacy III  Safety III

**Evidentiary Table (continued).**

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Weinstein et al <sup>69</sup>	1986	Blinded, crossover design; 101 anxious patients, mean 7.7 y; age range 3-12 y; ASA and gender not listed	Up to 40% N <sub>2</sub> O vs up to 40% N <sub>2</sub> in anxious children undergoing dental procedures	Behaviors videotaped and then scored with standard format; vital signs	N <sub>2</sub> O increased patients' positive response to suggestion and effect of reassurance; greater effect in older patients; more inappropriate movement in younger patients with N <sub>2</sub> O	Dental study; no data on safety	Efficacy I  Safety N/A
Wilson et al <sup>70</sup>	2002	Randomized, controlled, crossover trial; 44 patients, mean age 12.5 y; range 10-16 y; 16 male, 30 female (2 dropouts from study); ASA I; children NPO ≥2 h, undergoing dental extractions	Oral midazolam 0.5 mg/kg or 30% N <sub>2</sub> O	Blood pressure, heart rate, oxygen saturation, sedation and behavioral scores every 5 min; standardized anxiety levels and satisfaction scores	No difference in vital signs; N <sub>2</sub> O with higher oxygen saturations ( <i>P</i> <0.001); less time to maximum sedation ( <i>P</i> <0.001), faster recovery ( <i>P</i> <0.001); midazolam had deeper sedation, greater amnesia for painful events ( <i>P</i> <0.001); both reduced anxiety for second visit	Dental study; only 30% N <sub>2</sub> O studied; unclear who scorers were; appears to have been unblinded study	Efficacy II  Safety II
Wilson et al <sup>71</sup>	2003	Randomized, cross-over, controlled trial; 40 patients, mean 13.2 y; age range 12-16 y; ASA I/II; nothing by mouth ≥2h, undergoing orthodontic dental extractions	Intravenous midazolam titrated to effect (mean dose 2.8 mg) or 30% N <sub>2</sub> O	Standardized behavior and sedation scales; vital signs; oxygen saturation	Median time to maximum sedation 8 min for midazolam, 6 min for N <sub>2</sub> O ( <i>P</i> <0.001); for recovery 52 min for midazolam, 23 min for N <sub>2</sub> O ( <i>P</i> <0.0001); similar minimal changes in vital signs/oxygen saturations; depth of sedation and amnesia similar for both midazolam and N <sub>2</sub> O; 51% preferred midazolam, 38% N <sub>2</sub> O, 11% no preference	Dental study; only 30% N <sub>2</sub> O studied; anxiety and behavioral assessments by unblinded scorer	Efficacy II  Safety II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Luhmann et al <sup>72</sup>	2001	Partially blinded, prospective, randomized, controlled trial; 204 patients, mean age 4.1 y; age range 2-6 y; 66% boys; ASA I (92%), ASA II (8%)	Oral midazolam, 50% N <sub>2</sub> O or midazolam+N <sub>2</sub> O (control=no sedation) during ED facial laceration repair; fasted ≥2 h; local anesthetics used	OSBD-R from videotapes and VAS by observers for distress; recovery time; vital signs, oxygen saturation; adverse events defined	Less distress with N <sub>2</sub> O during lidocaine injection, cleaning, suturing; ( $P=0.0001$ , each interval); midazolam+N <sub>2</sub> O not better than N <sub>2</sub> O alone; no major adverse events; minor adverse events (ataxia) more frequent with midazolam except vomiting (10% with N <sub>2</sub> O)	Small sample size for serious adverse events	Efficacy I  Safety I
Burton et al <sup>73</sup>	1998	Double-blinded, randomized, placebo-controlled trial in ED; 30 patients enrolled, mean age 3.8 y, 17 got N <sub>2</sub> O; ASA and gender not listed	50% N <sub>2</sub> O vs 100% oxygen (continuous flow apparatus) during laceration repair in anxious children 2-7 y; NPO ≥2 h; local anesthetic used	CHEOPS at bedside, anxiety scale, patient co-operation; vital signs, oxygen saturation	Study stopped when planned halfway review found significant efficacy: N <sub>2</sub> O reduced behavioral distress and anxiety ( $P<0.0001$ , each); 1 patient (6%) vomited, 2 (12%) were deeply sedated, 4 (24%) had transient dizziness; no major adverse events	Small sample size; use of mask with oxygen in controls may have increased patient anxiety, thus enhancing apparent N <sub>2</sub> O benefit	Efficacy I  Safety II
Gamis et al <sup>74</sup>	1989	Prospective, double-blinded, randomized, controlled trial in ED; 34 patients, mean age around 7 y; 15 received N <sub>2</sub> O	30% N <sub>2</sub> O vs oxygen placebo for children 2-16 y of age undergoing laceration repair; local anesthesia used	CHEOPS before and during repair; subjects monitored with vital signs, oxygen saturation	Patients >8 y had less distress during suturing ( $P<0.05$ ); patients <8 y had trend toward less distress with N <sub>2</sub> O but did not reach significance; no emesis, hypoxia, oversedation, or adverse events	Small sample size; N <sub>2</sub> O 30%; use of mask with oxygen in controls may have increased patient anxiety, thus enhancing apparent N <sub>2</sub> O benefit	Efficacy II  Safety II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Keidan et al <sup>65</sup>	2003	Nonrandomized trial in consecutive nonfasted children in ED undergoing painful procedures	50% N <sub>2</sub> O during procedure, administered by anesthetist	Pain 10-point VAS by anesthetist, ED physician, RN, and parent during procedure; major and minor adverse events recorded; vital signs and oxygen saturation	55 children (4 refusals); ages 0.5-15 y completed procedures (intravenous, lumbar puncture, laceration repairs, fracture reduction, burn management, joint aspiration), some augmented by local anesthesia; procedure time mean 7 min; pain scores mean 1.4/10 for <3 y; 0.2/10 for >3 y; vomiting 9%; euphoria 7%; prolonged recovery in 1; no significant adverse events	Small sample for safety regarding major adverse events	Efficacy II Safety II
Bar-Meir et al <sup>76</sup>	2006	Nonrandomized, nonblinded alternating trial in nonfasted children in the ED	50% N <sub>2</sub> O vs nothing during suturing of facial lacerations by plastic surgeon in ED; N <sub>2</sub> O initially administered by surgeon, then by RN or parent; patient monitored by RN	Efficacy measured by FLACC scale and need for restraint; safety measured by heart rate, oxygen saturation changes, major and minor adverse effects	60 children, mean age 3-4 y; 2/3 boys; FLACC (distress) scores less with addition of N <sub>2</sub> O during infiltration and suturing ( $P<0.01$ ); no major adverse effects, 11% had vomiting	Nonblinded trial; small sample size for safety regarding major adverse events	Efficacy III Safety II
Luhmann et al <sup>77</sup>	2006	Partially blinded randomized controlled trial; 102 patients, mean age 9 y; 60% boys; ASA I or II; age range 5-17 y	50% N <sub>2</sub> O+lidocaine hematoma block or intravenous ketamine 1 mg/kg, glycopyrrolate 5 ug/kg+midazolam 0.1 mg/kg, maximum 2 mg for reduction of forearm fractures in ED; both groups received oral oxycodone; fasted $\geq 2$ h	Procedural Behavior Checklist (from videotapes); time of recovery; VAS for observed pain/distress/satisfaction; vital signs, oxygen saturation; adverse events in ED and 1 day afterward	Less distress for N <sub>2</sub> O/hematoma block ( $P=0.02$ ) but change very small for both groups; recovery time much less for N <sub>2</sub> O/hematoma block ( $P<0.0001$ ); minor adverse effects more frequent for ketamine/midazolam in ED ( $P=0.0003$ ) and at 24 h ( $P=0.04$ ); all easily managed	Respiratory distress not measured by ET/CO <sub>2</sub> ; use of local anesthetic	Efficacy I Safety I

**Evidentiary Table (continued).**

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome/Criterion Standard	Results	Limitations/Comments	Class
Evans et al. <sup>78</sup>	1995	Prospective randomized controlled trial in children 4-16 y with fractures in orthopedic clinic; 30 patients, 4-15 y; average age 10 y; 19 boys; ASA not listed	50% N <sub>2</sub> O (fixed dose) (N=15) vs intramuscular meperidine 2 mg/kg/promethazine 1 mg/kg (N=15) for fracture reduction	CHEOPS during reduction (at bedside); patient memory/satisfaction scores (done at first follow-up); monitoring vital signs, observation, no oximetry	No difference in CHEOPS (~9.5/13) during reduction or memory/satisfaction scores at 30 min post-reduction; recovery time 30 min (N <sub>2</sub> O) versus 83 min (meperidine/promethazine) ( <i>P</i> < 0.01); no nausea, vomiting, or hypoxia	Orthopedic clinic patients; small sample size; mixed fracture types; no oxygen saturations	Efficacy II Safety III
Gregory and Sullivan <sup>79</sup>	1996	Nonrandomized (alternating), prospective trial for forearm fracture reduction in children ≥4 y; 28 patients; in N <sub>2</sub> O group mean age 7.9 y; Bier block mean age 9.3 y; 16 boys, 12 girls; ASA not listed; ED setting	50% N <sub>2</sub> O vs intravenous regional anesthesia (Bier block); no additional pain or sedative medications within 4 h	Completion of reduction; postreduction subjects completed Wong-Baker Faces Scale for pain, summing all aspects of treatment of fracture; patients >8 y and providers also completed pain VAS; vital signs, oxygen saturation	Mean Wong-Baker Faces score 3.5/6 for N <sub>2</sub> O, 3.6/6 for Bier block; similar results for VAS; successful reduction in 27/28 fractures; 1 technical failure with Bier block; no nausea, vomiting, desaturation, or adverse event; 41 min total time for N <sub>2</sub> O vs 61 min for Bier block ( <i>P</i> <0.0003)	Small sample size (N=14) in each group, total 28 patients	Efficacy II Safety II
Hennrikus et al. <sup>80</sup>	1994	Nonrandomized trial; unfasted children >4 y for reduction of closed fractures in ED; 54 patients; 36 boys, 18 girls; no ASA listed; average age 8.8 y; fractures	Fixed 50% N <sub>2</sub> O; no additional pain or sedative medications	CHEOPS by observing physician; pain recalled by subject (4-point scale); vital signs, oxygen saturation	5 patients failed analgesia (no effect); average CHEOPS 9/13 (moderate pain), 46% ≥10 (significant pain); recalled pain: 42% moderate-to-severe; no vomiting, desaturation; 2 unsuccessful reductions because of residual malalignment		Efficacy II Safety II

**Evidentiary Table (continued).**

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Hennrikus et al <sup>81</sup>	1995	Prospective, nonrandomized trial; 100 patients, average age 9 y, mostly forearm fractures; unfasted children >4 y for reduction of closed fractures in ED; age range 4-17 y; 68 boys, 32 girls; no ASA listed	Fixed 50% N <sub>2</sub> O and lidocaine fracture hematoma block; no additional pain or sedative medications	CHEOPS by observing physician; pain recalled by subject on 10-point Faces scale; vital signs, oxygen saturation	3 children with no effect; 52% CHEOPS ≤6 (no pain); 13% CHEOPS ≥10 (severe pain); 81% amnestic for hematoma block and reduction; no vomiting, no adverse event; 3 unsuccessful reductions due to residual malalignment; higher proportion failures with displaced radius/ulna fracture	Nonblinded	Efficacy II  Safety II
Wattenmaker et al <sup>82</sup>	1990	Prospective cohort, nonrandomized trial, unpremedicated children >4 y; 22 patients, average age 10 y; range 4-15 y; ASA and gender not listed	Fixed 50% N <sub>2</sub> O for fracture reduction in ED; fractures chosen expected to require single reduction attempt	Informal analgesia effectiveness scale (severe, moderate, minimal, no pain); vital signs	Fractures: 18 angulated or displaced forearm, 2 displaced proximal phalangeal, 1 angulated tibia/fibula; 1 displaced humerus; 20/22 fractures reduced; 52% minimal, 38% moderate, 10% no pain; 60% recalled no pain; no complications with N <sub>2</sub> O	Small sample size, informal observer pain scale	Efficacy III  Safety III
Burnweit et al <sup>83</sup>	2004	Nonrandomized trial in selected healthy children 1-20 y of age, undergoing minor painful procedures by pediatric surgeon in outpatient "minor operating room"	50% N <sub>2</sub> O administered by specially trained RN; EMLA then buffered lidocaine 1% with epinephrine local anesthetic; parent at bedside	Wong-Baker Faces Scale by patient to measure pain before, during, and after procedure; vital signs and oxygen saturation monitored throughout	150 children ages 1-20 y, mean age 9.8 y; 57% girls; 40 had excision of nevi/cysts, 34% had abscess incision and drainage; mean Wong-Baker scores ≤0.5/6 during procedure; 2 vomited, 2 others nauseated (3% total); no major adverse events	Selection criteria for patients not stated; small sample for safety regarding major adverse events	Efficacy II  Safety II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Ekbom et al <sup>84</sup>	2005	Randomized controlled trial in 50 children, mean age 13 y, and crossover trial in 20 anxious children, mean age 11 y; all ASA I, ages 6-18 y; nothing by mouth $\geq$ 4 h, undergoing venous cannulation in outpatient clinic	EMLA $\pm$ N <sub>2</sub> O titrated to 50% for intravenous placement	Pain VAS by patient 5 min after cannulation, parent and patient global evaluation on 5-point linear scale, RN overall assessment of distress on 3-point scale, time and number of attempts for cannulation, changes in heart rate and oxygen saturations, other adverse effects	N <sub>2</sub> O + EMLA resulted in fewer attempts, less pain, same overall time, and greater satisfaction (all $P < 0.001$ ) compared to EMLA alone; 90% of patients who experienced both treatments preferred N <sub>2</sub> O+EMLA over EMLA alone; no significant adverse events, 1 patient with brief tinnitus	Fasted, planned procedures; weak indirect measure of distress	Efficacy II Safety II
Henderson et al <sup>85</sup>	1990	Blinded, placebo-controlled, randomized, controlled trial in children 3 wk to 18 y of age; 165 ASA I patients; gender not listed	50% N <sub>2</sub> O, 70% N <sub>2</sub> O, 100% oxygen, or air for analgesia during venous cannulation before elective surgery; no preanesthetic medications given	CHEOPS pain score during intravenous attempt by blinded observer; vital signs, oxygen saturation	No pain behavior in 56% with 50% N <sub>2</sub> O ( $P < 0.05$ ); no pain behavior in 77% with 70% N <sub>2</sub> O ( $P < 0.05$ ) vs 16% with oxygen, 15% with air; adverse events (excitement, dysphoria, nausea, restlessness, opisthotonic movements in 1 child) in 28% with 70% N <sub>2</sub> O; no adverse events in other groups ( $P < 0.05$ )	Fasted patients in the operating room; small sample size; 1 group (air) had no mask, other 3 groups had mask	Efficacy II Safety II
Kanagasundaram et al <sup>86</sup>	2001	Nonrandomized trial, oncology clinic patients; 90 patients, mean age 7 y; fasted children; painful procedures: intravenous start, bone marrow aspiration, lumbar puncture, or dressing change; no gender or ASA listed	50-70% N <sub>2</sub> O; imagery, distraction, etc, taught preprocedure; parents present; no premedications	OSBD-R multiple phases: defined adverse events; depth of sedation analyzed by ages: 1-5, 5-10, >11 y; vital signs, oxygen saturation	N <sub>2</sub> O maintained low levels of distress during procedures; younger children had greater distress ( $P = 0.001$ ); deepest level of sedation=awake (able to communicate) in 93%; vomiting in 8%, desaturation <95% in 9%	Oncology clinic patients	Efficacy II Safety II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Annequin et al <sup>87</sup>	2000	Prospective cohort; multicenter; 31 centers; N <sub>2</sub> O provided outside operating room (outpatient clinics, hemato-oncology, ED); ages ≤18 y; 1,019 sedations; ages ≤18 y, median 6.4 y; 51% lumbar puncture/bone marrow aspirations in hemato-oncology patients; 21% lacerations in ED; gender and ASA not listed	Standard questionnaire after each N <sub>2</sub> O administration for 2 mo; fixed 50% N <sub>2</sub> O during lumbar puncture/bone marrow aspirations in hemato-oncology clinic patients, lacerations in ED patients; local anesthetics typically used	Self-assessment of pain (VAS) by patients >6 y and by nurses for all ages, occurrence of standard behavioral reactions, satisfaction by providers, monitored vital signs, direct observation	Overall median pain VAS 9/100 by patients, 1/10 by RNs and parents; staff satisfaction 88%; minor adverse effects in 37% (euphoria 20%, nausea/vomiting 4%, deep sedation 2%); no serious adverse effects	No oxygen saturation, no categorization of adverse effects; no standard protocol for N <sub>2</sub> O administration, use of adjunct medications or patient monitoring	Efficacy III Safety II
Keidan et al <sup>88</sup>	2005	Randomized, controlled trial; 47 patients, mean age 6 y; ages 3-15 y; 89% girls; 85% ASA I; setting: radiology unit	Oral midazolam (N=24) or continuous flow 50% N <sub>2</sub> O (N=23) during elective voiding cystourethrography; fasted children	Sedation AVPU scale, FLACC score (non-blinded), OSBD, VAS, defined adverse events; vital signs, oxygen saturation	Efficacy of sedation, anxiety, amnesia comparable; N <sub>2</sub> O patients required less restraint P(=0.01); recovery for N <sub>2</sub> O significantly faster (P<0.001); adverse effects minimal	Elective radiologic procedure: voiding cystourethrography; fasted children; small sample size	Efficacy II Safety II
Sundin et al <sup>89</sup>	1981	Nonrandomized trial in 20 healthy non-pregnant volunteers of both sexes 18-60 y of age; ASA not listed	N <sub>2</sub> O titrated to effect to study anxiolytic effects of N <sub>2</sub> O	Blood pressure, heart rate, ECG, salivary and blood cortisol, standardized sensation to pain (sandpaper), degree of sedation, psychologic screening inventory	Concentration of N <sub>2</sub> O to achieve anxiolytic effect ranged from 25%-65%, averaging 35%-40%; no analgesic effect found at anxiolytic level; report of anxiolysis correlated with salivary cortisol, diastolic blood pressure	Adult volunteers, relatively low anxiety at baseline; nasal administration with room air entrained; small sample size	Efficacy III Safety III

**Evidentiary Table (continued).**

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Frampton et al <sup>90</sup>	2003	Nonrandomized trial in consecutive healthy children in ED, >12 mo of age, fasted $\geq 2$ h, undergoing painful procedure	50-70% N <sub>2</sub> O administered by specially trained RN	State of consciousness, respirations, airway patency, and oxygen saturation monitored; pain or distress not measured; major and minor adverse events defined and recorded	224 children (113 <5 y) completed (1 failure due to vomiting); procedures included laceration repair/wound management, intravenous placement, lumbar puncture, fracture reduction, burn management; mean N <sub>2</sub> O administration time 14 min; one 18-mo old with recent bronchiolitis had brief tachypnea without decrease in oxygen saturation, 8% had vomiting, 1% had dysphoria	Patients with upper respiratory infection, respiratory symptoms, asthma, or received intravenous opioids or sedatives were excluded for sedation; small sample for safety regarding major adverse events	Efficacy N/A  Safety II
Cleaton-Jones <sup>91</sup>	1976	Prospective cohort (healthy, nonfasted dental students); 14 students, ages 22-29 y, mean 23.6 y: ASA and gender not listed	After 5 min of 50% N <sub>2</sub> O while supine on a radiograph table, 10 mL of radiopaque dye was placed on the posterior tongue and swallowed	Dye on chest radiograph at 1 and 5 min after swallowing dye; vital signs	No physiologic changes; no dye seen in larynx, trachea, or lungs; dye seen in lower esophagus of all	Small sample size; subjects not having dental procedure; brief N <sub>2</sub> O	Efficacy N/A  Safety III
Dollfus et al <sup>92</sup>	1995	Prospective cohort; cancer patients in oncology clinic, many had several N <sub>2</sub> O sedations at different times; 87 patients, 200 procedures; average age 8.5 y (9 mo-18 y); ASA class and gender not listed	50% N <sub>2</sub> O (fixed dose, self administration) for lumbar puncture/bone marrow aspiration; patients fasted $\geq 4$ h, no premedication; EMLA, then lidocaine injected at site	Efficacy: pain 10-point VAS by patient if >5 y and by observer using 4-point scale; operator satisfaction scale; compared to memory of previous pain for lumbar puncture/bone marrow aspiration without N <sub>2</sub> O (VAS estimates) to those with N <sub>2</sub> O	8 patients refused mask; for 29 pairs of self-evaluation: lumbar puncture pain 7.96 without vs 1.49 with N <sub>2</sub> O, bone marrow aspiration pain 7.44 without vs 1.86 with N <sub>2</sub> O ( $P<0.0001$ ); operator satisfaction 97%; minor adverse effects in 27%, transient (euphoria/dysphoria 21, vomiting 3); no major adverse events	Hematology/oncology clinic patients; comparison to procedure without N <sub>2</sub> O dependent on memory of previous procedure	Efficacy III  Safety III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome/Criterion Standard	Results	Limitations/Comments	Class
Dunn-Russell et al <sup>93</sup>	1993	Prospective crossover trial in children requiring 2 dental procedures; 24 ASA I patients ages 3.4-9.4 y, mean 5.6 y; gender not listed	Compared initial 5 min of recovery with 100% oxygen versus room air after 40% N <sub>2</sub> O sedation; fasted ≥2 h	Oxygen saturation at 1.5-second intervals for 5 min after stopping of N <sub>2</sub> O	Mean time of 40% N <sub>2</sub> O exposure was 28-29 min; oxygen saturations fluctuated <1% for both groups; statistically but not clinically significant	Dental study: no pre- or concurrent additional medications, only 40% N <sub>2</sub> O studied	Efficacy N/A  Safety II
Gerhardt et al <sup>94</sup>	2001	Double-blinded, placebo-controlled, randomized, controlled trial; crossover design; healthy adult volunteers 18-50 y, ASA gender not listed; ED military teaching hospital	50% N <sub>2</sub> O vs 100% oxygen for reduction of pain and anxiety during venous cannulation (18 gauge) in healthy adult volunteers	Change in subject VAS (100 mm) for pain and anxiety between baseline and IV cannulation; measured after each cannulation	11 subjects, 1 withdrew because of dizziness with N <sub>2</sub> O; mean pain less with N <sub>2</sub> O (VAS 10 for N <sub>2</sub> O, 31 for control) ( $P=0.01$ ), and anxiety (0.5 for N <sub>2</sub> O, 15 for control) less with N <sub>2</sub> O ( $P=0.02$ )	Only adults studied, small sample size (N=10)	Efficacy III  Safety N/A
Roberts and Wignall <sup>95</sup>	1982	Nonrandomized, prospective comparison; 50 children, mean ages 13 y 2 mo sedated, 12 y 9 mo controls, age range 4-18 y; ASA and gender not listed	Children undergoing dental procedures, non-sedated vs sedated with N <sub>2</sub> O titrated to effect (for anxious patients); N <sub>2</sub> O concentration varied 20%-65% (23 patients got <50%); radiopaque dye placed on posterior tongue after sedation before drilling, halfway through procedure, and at end before recovery	Chest radiograph findings of intrapulmonary dye; respiratory symptoms posttreatment	No respiratory problems in days or weeks posttreatment; neither group aspirated dye	Dental procedures; no standard N <sub>2</sub> O concentration	Efficacy N/A  Safety II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Rubin et al <sup>96</sup>	1977	Prospective, crossover trial; 10 healthy, fasted, nonpregnant female adult volunteers, ages 18-21 y	During 50% N <sub>2</sub> O sedation for more than 10 min water sprayed to simulate dental procedure, then 15 mL of radiopaque dye dripped over 2 min onto back of tongue; process repeated 1 week later except without N <sub>2</sub> O	Chest radiograph to look for aspirated dye read by radiologist blinded to study purpose; pulse monitored	In 2 of 10 (20%), dye seen in lungs on chest radiograph after N <sub>2</sub> O; no dye seen after procedure without N <sub>2</sub> O; not statistically significant (0.4 < P < 0.5)	Dental study simulated; very small sample size; 20% with aspiration may be clinically significant	Efficacy N/A  Safety II
Onody et al <sup>97</sup>	2006	Government mandated survey (questionnaire) including adverse event report for each of 35,828 non-operating room administration of N <sub>2</sub> O over 4 y period; questions open-ended; adverse event not defined	50% N <sub>2</sub> O for nondental procedures	Open-ended questionnaire	35,942 usages, 114 missing data; 35,828 analyzed; 82% in pediatric patients; 3% 0-1 y, 23% 1-4 y, 35% 5-10 y, 22% 11-18 y; 4% overall adverse events; 46% gastrointestinal (nausea/vomiting), 41% agitation/euphoria; adverse event frequency increased with increasing age; serious adverse event in 0.08%, half associated with additional drug; serious adverse event percentage thought due to N <sub>2</sub> O=0.03% (3/10,000 N <sub>2</sub> O administration); serious adverse event included bradycardia, nightmares, headache, sweating; cardiac arrest, laryngospasm, seizures reported but thought not due to N <sub>2</sub> O	Open-ended style likely led to under reporting of minor effects such as euphoria, somnolence; no information on fasting status, location; only type of procedure reported; no details on life-threatening adverse event thought not due to N <sub>2</sub> O	Efficacy N/A  Safety III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Gall et al <sup>99</sup>	2001	Prospective cohort, multicenter (46 institutions), most in EDs and oncology clinics; age ≤18 y, gender and ASA not listed	18-mo review of standardized records of 50% N <sub>2</sub> O in children	Major adverse events defined: airway obstruction, apnea, desaturation, cardiac changes, loss of verbal contact	7,511 patients (2,095 in ED for laceration repair, fracture reduction, abscess incision and drainage); 75 (1%) failed sedation; major adverse events 0.33%, all brief, no airway interventions; increased major adverse event if patient age <1 y ( $P=$ .001) or if opioid+benzodiazepine also given ( $P=$ .04)	Unclear how patients monitored, eg, oxygen saturations, vital signs	Efficacy N/A Safety II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Rowland et al <sup>101</sup>	1992	Retrospective cohort	Questionnaire of full-time female dental assistants who had been pregnant within past 4 y not due to birth control failure; 418 (91% response rate); ages 18-39 y, randomly chosen from California Registry	Relationship between exposure to N <sub>2</sub> O and fertility (number of menstrual cycles without contraception needed to become pregnant)	Each h of exposure to unscavenged N <sub>2</sub> O per week corresponded to 6% reduction in conception with each menstrual cycle; no relation to scavenged N <sub>2</sub> O; 60% reduction in fertility with ≥5 h per week exposure to unscavenged N <sub>2</sub> O; 50% of pregnancies spontaneously aborted with unscavenged ≥5 h per week vs 8% with scavenged N <sub>2</sub> O	Actual exposure to N <sub>2</sub> O not measured; recall bias	Efficacy N/A  Safety (for health care providers) III
Rowland et al <sup>102</sup>	1995	Retrospective cohort	Questionnaire of full-time female California dental assistants who had been pregnant within past 4 y not due to birth control failure; current pregnancies through week 20 included 4,856 (69%) responded	Relationship between exposure to N <sub>2</sub> O and spontaneous abortions; person-week model	101 pregnancies (7%) ended in spontaneous abortion: higher risk of spontaneous abortion if working with unscavenged N <sub>2</sub> O ≥3 h per week; relative risk 2.6; no increase with scavenged N <sub>2</sub> O	Actual exposure to N <sub>2</sub> O not measured; recall bias	Efficacy N/A  Safety (for health care providers) III
Ahlborg et al <sup>103</sup>	1996	Retrospective survey in 1989 of all Swedish midwives born in 1940 or later	Queried working conditions within past 5 y, including exposure to N <sub>2</sub> O, and number of menstrual cycles during most recent successful attempt to become pregnant	Per-cycle probability of becoming pregnant calculated; ratio of exposed to unexposed to N <sub>2</sub> O compared	3,358 responses (84%); midwives working nights or 2 or 3 shift rotations had decreased fertility compared to day-shift-only workers; no effect of N <sub>2</sub> O except in those assisting at >30 deliveries per month when N <sub>2</sub> O was used; no correlation with use of scavenging	Recall bias; survey response dependent; only successful pregnancies queried; inability to conceive not included	Efficacy N/A  Safety (for health care providers) III

**Evidentiary Table (continued).**

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Axelsson et al <sup>104</sup>	1996	Retrospective; survey in 1989 of all Swedish midwives born in 1940 or later	Queried working conditions, including exposure to N <sub>2</sub> O during deliveries; midwives' spontaneous abortions for pregnancies between 1980-1988; current and ectopic pregnancies and women with ≥5 spontaneous abortions excluded	Association between work conditions, including exposure to N <sub>2</sub> O, and spontaneous abortions; exposure to N <sub>2</sub> O classified as none, used in ≤50% of deliveries, or used in >50% of deliveries	3,358 responses (84%); no association found between N <sub>2</sub> O use and midwives' spontaneous abortions (OR 0.95), including use during first trimester	Recall bias, survey response dependent; many could not recall if scavenger device used	Efficacy N/A  Safety (for health care providers) III
Brodsky et al <sup>105</sup>	1981	Questionnaire of N <sub>2</sub> O user and nonuser dentists and their assistants randomly selected from national registry	15,000 each, N <sub>2</sub> O user and nonuser dentists and their assistants, randomly selected; asked about h per week use of N <sub>2</sub> O during past 10 y and any symptoms of adverse effects; answers blindly reviewed; exposure to N <sub>2</sub> O during 10 y defined: <3,000 h=light, >3,000 h=heavy (3,000 h=6 h per week for decade); rates adjusted for mercury exposure	Answers grouped into (1) nerve specific symptom (eg, sciatica), (2) nonspecific nerve symptom (eg, numbness, paresthesia, weakness), (3) symptoms secondary to specific diseases (eg, multiple sclerosis, pernicious anemia), (4) miscellaneous (eg, migraine headache, stroke), and (5) no neurologic complaints	>18,000 responses (>70% each group); for dentists and assistants, vs no or light exposure, "heavy exposure" associated with group 2 symptoms (nonspecific neurologic symptoms) ( <i>P</i> <0.01), and group 3 symptoms (specific neurologic diagnosis) ( <i>P</i> =0.05); for assistants, group 1 symptoms also associated ( <i>P</i> =0.04)	Recall bias; responder bias (more symptoms reported if responder concerned N <sub>2</sub> O causes problems and responder has regular N <sub>2</sub> O exposure)	Efficacy N/A  Safety (for health care provider) III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Stevens et al <sup>107</sup>	2004	Meta-analysis	Evaluated 21 randomized controlled trials (1,616 patients) to determine the efficacy, effect of dose, and safety of oral sucrose in neonates	Numerous outcome measures were evaluated, and where possible, WMD with 95% CI were calculated for continuous outcome measures	Pooled PIPP scores across 3 randomized controlled trials were reduced in neonates given sucrose at 30 seconds after heel lance (WMD -1.64, 95% CI -2.47 to -0.81) and at 60 seconds after heel lance (WMD -2.05, 95% CI -3.08 to -1.02); pooled results for change in heart rate across 2 randomized controlled trials found no difference at 1 min or 3 min post-heel lance	Well-executed meta-analysis; excluded several studies for relatively minor flaws in accordance to their methodology, however, these studies would not have contradicted their conclusions	I
Rogers et al <sup>108</sup>	2006	Randomized controlled trial	Compared 2 cc of 24% sucrose or water 2 min before bladder catheterization in infants born >34 wk (n=80, 51 males, 29 females, PNA range 3-90 days); ED study	Primary outcome measures were: change in the composite DAN score from baseline to point of maximal catheter insertion, percentage of patients crying during procedure, and time to return to baseline behavior	Although there was a trend toward reduced signs of distress with sucrose, there was no significant difference between the 2 groups for change in DAN score, percentage of patients crying, and time to return to baseline behavior; post hoc subgroup analysis found a significant reduction in all outcome measures in the 1-to 30-day age group (DAN score 2.9 vs 5.3, $P=0.035$ ; percentage crying 29% vs 79%, $P=0.008$ ; return to baseline 10 vs 37 seconds, $P=0.04$ )	This is the only trial that takes place in the ED, and the only one that uses bladder catheterization as the painful stimulus; the study was downgraded because although there is some evidence that sucrose is less effective in older age groups, the study was not designed and powered for age-specific subgroup analysis; no adverse events were noted	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Stevens et al <sup>114</sup>	1999	Randomized controlled trial (crossover design)	Compared pacifier with 0.1 cc of 24% sucrose, pacifier with water, or prone positioning vs control during heel stick in very-low-birth-weight, preterm neonates (n=122, 70 males, 52 females, gestational age 28-29 wk, PNA 3-13 days); NICU study	Primary outcome measure was PIPP scores	Mean PIPP scores were: control 9.8, prone 10.3, pacifier with water 8.4, pacifier with sucrose 7.9 ( $P<0.0001$ ); post hoc analysis revealed a significant difference between the pacifier with sucrose and control ( $P<0.0001$ )	Lack of generalizability to the ED because of very-low-birth-weight, preterm infants; also multiple treatment groups, not all relevant to this critical question; no group received oral sucrose alone; no adverse events observed	III
Johnston et al <sup>115</sup>	1999	Randomized controlled trial	Compared a single dose of 0.05 cc of 24% sucrose vs repeated doses of 0.05 cc of 24% sucrose delivered before, during, and after the procedure, vs water in preterm neonates in the NICU undergoing heel stick (n=48, gestational age 30-31 wk, PNA 6-7 days); NICU study	Outcome measure was pain as measured on the PIPP composite scale	The group with repeated doses had significantly lower postprocedural PIPP scores compared with placebo ( $P<0.05$ ); the group with a single dose had lower PIPP scores than placebo, but the differences did not achieve statistical significance ( $P=0.07$ )	Limited generalizability to ED as study population was preterm infants receiving ongoing care in the NICU	III
Gibbins et al <sup>116</sup>	2002	Randomized controlled trial	Compared 0.5 cc of 24% sucrose plus non-nutritive sucking, water plus non-nutritive sucking, or sucrose alone in preterm and term neonates after heel stick; SNAP-PE severity of illness score ranged from 4.00 to 4.68 (n=190, 94 males, 96 females, mean gestational age 33-34 wks, mean PNA approximately 3 days); NICU study	Primary outcome measure was efficacy, as measured by the PIPP pain score that includes physiologic, behavioral, and contextual measures, and takes into account gestational age; the study also assessed safety, evaluating the incidence of adverse events	Mean PIPP scores differed among the sucrose and non-nutritive sucking group (8.16 at 30 seconds, 8.78 at 60 seconds), the sucrose alone group (9.77 at 30 seconds, 11.20 at 60 seconds), and the non-nutritive sucking with water group (10.19 at 30 seconds, 11.20 at 60 seconds), $P<0.001$ ; post hoc analysis found that the sucrose plus non-nutritive sucking group had lower scores than the other treatment groups; sucrose alone and non-nutritive sucking with water were not significantly different from each other; adverse events (5 episodes of desaturation and 1 of choking) were too rare to perform statistical comparisons among the groups	Limited external validity; findings in this study population (premature infants receiving care in NICU) may not generalize to neonates in the ED; did not have "no treatment" control group because of ethical considerations; the study was not powered to detect the influence of gestational age on the efficacy of sucrose	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Isik et al <sup>117</sup>	2000	Randomized controlled trial	Compared 2 cc of 30% sucrose, 30% glucose, 10% glucose or water 2 min before heel stick in healthy, full-term neonates (n=113, 56 males, 57 females, median gestational age 40 wk, median PNA 2 days); university hospital setting	Outcome measures: crying time during 3-min period after heel lance, maximum heart rate, percentage change in heart rate from baseline at min 1, 2, and 3, and heart rate recovery time	Mean crying time: 61 seconds in the 30% sucrose group, 103 seconds in the 10% glucose group, 95 seconds in the 30% glucose group, and 105 seconds in the control group ( $P=0.02$ overall, $P=0.002$ for sucrose versus water); there was a lower percentage change in heart rate in the sucrose group at 2 min postprocedure ( $P=0.05$ ); differences in maximum heart rate and heart rate recovery time did not differ among groups	No primary outcome measure clearly defined; also multiple comparisons were made at various time points without using repeated measures analysis; did not report adverse events	II
Haouari et al <sup>118</sup>	1995	Randomized controlled trial	Compared 2 cc of 12.5%, 25%, and 50% sucrose solution vs control in full-term, healthy newborns undergoing heel stick (n=60, 29 males, 31 females, median gestational age 38-39 wk, median PNA 3-4 days); postnatal ward setting	Primary outcome measure was duration of crying during the first 3 min after heel stick; additional outcome measures included duration of first cry, percentage change in heart rate and SpO <sub>2</sub> after heel stick, and change in facial expression on 5-point scale	There was a significant reduction in crying time (from 135 seconds to 45 seconds) and duration of first cry (from 95 seconds to 20 seconds) in the 50% sucrose group compared with controls (both $P=0.02$ ); no differences in change in SpO <sub>2</sub> or facial expression among the groups	With only 15 infants per treatment group, the study may have been underpowered to determine the minimum effective sucrose dose; did not report adverse events	II
Abad et al <sup>119</sup>	2001	Randomized controlled trial	Compared the effect of water, EMLA cream, 2 cc of 24% oral sucrose, or both EMLA and sucrose in reducing the pain of venipuncture in stable, full-term neonates (n=51, 38 males, 13 females, mean gestational age 38.6-40.0 wk, mean PNA 1.8-2.0 days); neonatal unit setting	Primary outcome measure was reduction in audible crying time postprocedure; secondary outcome measure was change in vital signs (heart rate, respiratory rate, and SaO <sub>2</sub> )	Sucrose reduced crying time relative to placebo ( $P=0.001$ ); EMLA plus sucrose also reduced crying time relative to water ( $P=0.008$ ); overall, there was a significant change in heart rate (increase), respiratory rate (increase), and SaO <sub>2</sub> (decrease) to venipuncture, but only heart rate actually differed among treatment groups; it was significantly lower in the sucrose group ( $P=0.03$ ) and EMLA plus sucrose group ( $P=0.04$ )	A subset of infants (n=4) was enrolled twice and was quasi-randomized to a different treatment group for the second venipuncture	II

**Evidentiary Table (continued).**

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Gormally et al <sup>120</sup>	2001	Randomized controlled trial	Compared the effect of 0.75 cc of 24% sucrose alone, holding alone, sucrose plus holding, vs control in reducing pain during heel stick in healthy, full-term newborns (n=85, 38 males, 47 females, mean gestational age 39.5 wk, mean PNA 53-63 h); community hospital setting	Outcome measures: percentage of time crying during min 1, 2, and 3 of the procedure, the Pain Concatenation Score, heart rate, and vagal tone	There was a significant reduction in mean percentage of time crying in the sucrose group compared with water ( $P<0.05$ ); the effect of holding on crying was not significant; in contrast, holding caused a significant reduction in the Pain Concatenation Score ( $P<0.02$ ), but sucrose did not; heart rate and vagal tone did not differ significantly among groups	Multiple main outcome measures; also, initially NFCS was one of the planned outcome measures but because of difficulties seeing and grading facial expressions, it was changed to the Pain Concatenation Score; heel stick was performed by 1 of 8 nurses; mean duration of procedure was similar across groups, but the number of heel squeezes required to obtain blood was higher in the sucrose-alone group, which subsequent ANCOVA analysis identified as a possible confounder; did not report adverse events	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Greenberg <sup>121</sup>	2002	Randomized controlled trial	Compared pacifier plus water, pacifier plus table sugar (sucrose), 2 cc of 12% sucrose by syringe, or control during heel stick in healthy, full-term neonates (n=84, 38 males, 46 females, gestational age >37 wk, mean PNA 18 h); moderate-sized hospital study	Outcome measures: duration of cry, vagal tone index as calculated from heart rate variability, and salivary cortisol	Duration of cry differed significantly among groups ( $P=0.001$ ); the $P$ value of the difference between the 12% sucrose group (85 seconds) and control (133 seconds) was not reported; post hoc analysis found that infants in the pacifier plus table sugar group had shorter duration of cry (46 seconds) than the pacifier plus water group (126 seconds, $P=0.006$ ), and the control group ( $P=0.001$ ); vagal tone index differed significantly among groups ( $P=0.005$ ); post hoc analysis group found that the pacifier plus table sugar group had a significantly lower index than control during the procedure and certain postprocedural time periods; no differences in salivary cortisol levels among groups	No primary outcome measure identified; not all $P$ values reported; 12% sucrose might have been suboptimal concentration for comparison; clinically relevant and practical research question as table sugar easily stored and readily available; did not report adverse events	II
Ors et al <sup>122</sup>	1999	Randomized controlled trial	Compared 2 cc of 25% sucrose, human milk, or water prior to heel stick in healthy, full-term neonates (n=102, 49 males, 53 females, median gestational age 39-40 wk, median PNA 1.6 days); university hospital study	Outcome measures: crying time, percentage change in heart rate, and time to "recovery" of normal heart rate	Median crying time in the sucrose group was shorter than in the milk or water group (36 seconds vs 62 seconds vs 52 seconds, $P=0.0009$ ); median heart rate recovery time in the sucrose group was shorter than in the milk or water group (72 seconds vs 112 seconds vs 124 seconds, $P=0.004$ ); percentage change in heart rate was significantly lower in the sucrose groups at 1 min, 2 min, and 3 min ( $P=0.008$ , $P=0.01$ , $P=0.002$ )	Non-ED population; no primary outcome measure was identified	II
Allen et al <sup>123</sup>	1996	Randomized controlled trial	Compared effect of 2 cc of 12% sucrose vs water or no intervention prior to intramuscular vaccinations in healthy, full-term 2-wk to 18-mo-old infants (n=285); ambulatory pediatric clinic setting	Outcome measure: reduction in "audible distress vocalization" per 15 second interval after the immunization procedure	Among 2-wk-olds, both the sucrose group and the water group cried less than the no-intervention group after intramuscular injection ( $P<0.01$ , $P<0.01$ for pairwise comparison, respectively); neither the water nor sucrose group cried less than the no-intervention group in the 2-, 6-, 9-, 15-, or 18-mo-old groups	Number of patients in the treatment vs control groups was not specified; one of the few articles to assess sucrose in older infants	II

**Evidentiary Table (continued).**

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Ogawa et al <sup>124</sup>	2005	Randomized controlled trial, 2x2 design	Compared heel stick or venipuncture with or without 1 cc of 50% sucrose in healthy full-term neonates (n=100, 52 males, 48 females, mean gestational age 39-40 wk, PNA approximately 5 days); NICU study	Outcome measure: pain at specified points throughout and after the procedures as measured using the NCFS scale and cry duration	Oral sucrose significantly reduced NCFS scores during blood sampling by heel stick (58 seconds vs 47 seconds, $P<0.01$ ), and while the bleeding was being stopped (52 seconds vs 32 seconds, $P<0.01$ ); sucrose did not significantly affect NCSF scores during blood sampling by venipuncture; oral sucrose reduced neither the duration nor incidence of crying in the heel stick or venipuncture group	Primary study question was whether venipuncture or heel stick was more painful for neonates; no adverse effects were observed in any of the infants	II
Carbajal et al <sup>125</sup>	1999	Randomized controlled trial	Compared no treatment, water, 2 cc of 30% glucose, 2 cc of 30% sucrose, a pacifier, or 30% sucrose plus a pacifier in a convenience sample of normal, full-term neonates undergoing venipuncture (n=150, 88 males, 62 females, median gestational age 39-40 wk, median PNA 3-4 days); maternity ward setting	Primary outcome measure was pain as measured by the DAN scale	Mean pain scores: 7 no treatment, 7 water, 5 glucose, 5 sucrose, 2 pacifier, 1 pacifier and sucrose; compared with water, the median reduction in pain with sucrose was 2 (95% CI 0-4; $P=0.01$ ); compared with a pacifier, the median reduction in pain score with sucrose plus a pacifier was 1 (95% CI 0-2; $P=0.06$ )	Relatively small number of patients per group resulted in wide CIs around estimates of treatment effect; observers could not be blinded to presence of pacifier, and these groups showed the greatest effect; no adverse events were noted in any group	II
Guala et al <sup>126</sup>	2001	Randomized controlled trial	Compared 2 cc of 5%, 33%, or 50% sucrose solutions vs control prior to heel stick in healthy, full-term newborns (n=140, gestational age 38-41 wk, PNA 4 days); postnatal ward setting	Primary outcome measure was heart rate before, during, and after the procedure	Differences among groups were not statistically significant; no adverse effects were observed	The only outcome measure was heart rate, which does not appear to be a very consistent or sensitive measure of degree of pain; it would be preferable to use composite outcome measure	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Abad et al <sup>127</sup>	1996	Randomized controlled trial	Compared 2 cc of water, 2 cc of 12% sucrose, or 2 cc of 24% sucrose prior to venipuncture in healthy, preterm neonates (n=28, 15 males, 13 females, median gestational age 34.4 wk, median PNA 4 days); NICU study	Outcome measures: time spent audibly crying, and change in vital signs (heart rate, respiratory rate, and SpO <sub>2</sub> )	Time spent crying was significantly different among groups: 72.9 seconds in the control group, 63.1 seconds in the 12% sucrose group, and 19.1 seconds in the 24% sucrose group ( $P=0.026$ ); post hoc analysis revealed that 24% sucrose group cried significantly less than 12% sucrose and controls ( $P<0.05$ ); of vital sign outcomes, only heart rate was found to differ significantly among groups, with a lower heart rate at all time points in the 12% sucrose group	Limited external validity; findings in this study population (premature infants receiving longer-term care in NICU) may not generalize to neonates presenting to the ED	II
Acharya et al <sup>128</sup>	2004	Randomized controlled trial (crossover design)	Compared 2 cc of 25% sucrose versus water prior to venipuncture in healthy, preterm infants (n=39, 22 males, 17 females, mean gestational age 30.5 wk, mean PNA 27.2 days); NICU study	Outcome measures: crying time, NFCS, heart rate, and SpO <sub>2</sub>	Duration of first cry was 34 seconds shorter in the sucrose group (95% CI 16-51) and total duration of crying was 41 seconds shorter (95% CI 19-62); NFCS increased less in the sucrose group between baseline and after venipuncture (mean difference 2.4; 95% CI 1.3-3.5); mean heart rate increase from baseline to after venipuncture was lower in the sucrose group by 4.2 (95% CI 0.3-8.0); no difference in SpO <sub>2</sub>	Limited external validity; findings in this study population (premature infants receiving longer-term care in NICU) may not generalize to neonates presenting to the ED; no infant developed necrotizing enterocolitis	II
Bucher et al <sup>129</sup>	1995	Randomized controlled trial (crossover design)	Compared 2 cc of 50% sucrose or water given prior to heel stick in healthy, preterm infants (n=16, gestational age 27-34 wk, corrected PNA at time of study 33-36 wk); intermediate care setting	Primary outcome measures: change in heart rate from baseline, and duration of crying; secondary outcome measures: other physiologic variables (including cerebral blood flow) and duration of crying	Mean heart rate increase after the heel stick was 34 in the sucrose group and 51 in the water group ( $P=0.005$ ); percentage of time crying during the whole intervention was lower in the treatment group (72% vs 94%; $P=0.002$ ); recovery time in sucrose group was significantly shorter as measured by heart rate ( $P=0.05$ ) and respiratory rate ( $P=0.05$ ); there was no difference in effect on cerebral blood flow, oxygen saturation, and PCO <sub>2</sub> ; blinded nurses could not distinguish sucrose from water group	Limited external validity to ED population; all patients were premature in an inpatient, intermediate care setting (gestational age <35 wk); did not report adverse events	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Ramenghi et al <sup>130</sup>	1999	Randomized controlled trial (crossover design)	Compared 25% sucrose or water orally or by nasogastric tube 2 min before heel stick (n=30, median gestational age 34-35 wk, median PNA 3-4 days)	Primary outcomes: a composite, behavioral response score of 15 points, and percentage of time crying during 5-min observation period	There was significant reduction of behavioral score (5 vs 9, $P=0.002$ ) and percentage crying time (6 vs 22 seconds, $P=0.006$ ) in the intraoral sucrose group vs intraoral water; no significant difference in behavioral score or crying time when either solution was administered by nasogastric tube	Although designed primarily to address the question of the efficacy of nasogastric administration of sucrose, this study also compared the efficacy of intraoral sucrose vs water; external validity is limited by the fact that the study sample was comprised of preterm neonates being fed by nasogastric tube	II
Johnston et al <sup>131</sup>	1997	Randomized controlled trial	Compared 0.05 cc 24% sucrose, simulated rocking, or both, vs placebo in preterm, very-low-birth-weight neonates undergoing heel stick; mean SNAP-PE score ranged from 7.9 to 8.3 (n=85, 42 males, 43 females, mean PCA 31 wk, mean PNA 5 days); NICU study	Primary outcome measures: physiologic (heart rate and SpO <sub>2</sub> ) and behavioral (“facial actions”)	Both sucrose and sucrose plus rocking reduced facial expressions of pain ( $P<0.02$ ) but did not have an effect on heart rate; no significant difference between sucrose and sucrose plus rocking	Limited generalizability to ED as study population was very-low-birth-weight infants in NICU; used conservative dosing of sucrose in this population, which has been recommended by some authors; adverse events not reported	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Ramenghi et al <sup>132</sup>	1996	Randomized controlled trial	Compared 2 cc of 50% sucrose, 25% sucrose, nonsucrose sweetener, or water 2 min before heel stick in healthy term infants (n=60, median gestational age 38-39 wk, median PNA 3-4 days)	Outcomes measures: 5-point scale (determined by the presence of facial expressions and crying), crying during and after the procedure, and duration of first cry; heart rate was also recorded	There was no difference in pain score at time of heel stick, but it was higher in the water group than in other groups at 3 min (2 vs 0 in other groups; $P=0.05$ ); there was significant reduction in median duration of first cry and total percentage of time spent crying in all groups relative to water ( $P=0.02$ , $P=0.02$ ); percentage change in heart rate was significantly higher at 3 min postprocedure in the 50% sucrose and nonsucrose sweetener group vs water ( $P=0.009$ )	Use of unvalidated outcome measure; pain score was significantly higher in water group before heel stick, potentially influencing postprocedure pain scores	III
Blass <sup>133</sup>	1997	Randomized controlled trial	Compared heel stick after receiving either water, 2 cc of 12% sucrose, protein, lactose, dilute fat, concentrated fat, fat/lactose, Similac or Ross Special Formula (n=72, 30 males, 42 females, gestational age not specified but enrolled "normal newborns," PNA 22-40 h); community hospital setting	Outcome measure: percentage of crying during the procedure and during recovery	Sucrose and Similac were more effective than water in reducing the amount of crying during heel stick ( $P=0.015$ , $P=0.038$ ); water, Similac, and lactose were the only interventions that did not reduce crying during the recovery period; no $P$ value is provided for the effect of sucrose during the recovery period	Sample size was small given the large number of treatment groups; also, the study sought to assess a question of more academic than clinical interest; many of the substances tested are impractical for common use	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Blass and Hoffmeyer <sup>134</sup>	1991	Randomized controlled trial	2 distinct sections of study; both enrolled normal, full-term neonates, PNA 28-54 h; the first section compared sucrose (2 cc of 12%) with water before heel stick (n=24); the second section compared: no intervention, nipple with water, or nipple dipped in 24% sucrose during circumcision (n=30, 30 males); neonatal nursery setting	Outcome measure for the first section was percentage of time spent crying during the procedure and the 3-min recovery period; outcome measure for the second section was duration of crying during each phase of the procedure	12% sucrose reduced crying during and after heel stick compared with water ( $P<0.01$ ); pacifiers with sucrose were significantly more effective than pacifiers with water in reducing crying during circumcision ( $P<0.05$ ); pacifiers with either liquid were significantly more effective than no intervention ( $P<0.001$ )	Essentially 2 studies in 1 publication evaluating sucrose from a syringe in the heel stick section and sucrose from pacifier in the circumcision section; this resulted in smaller sample sizes for each component of the study; number of infants randomized to control vs treatment group not stated; circumcision is not an ED procedure	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Harrison et al <sup>135</sup>	2003	Randomized controlled trial	Compared 1 cc 33% sucrose (after publication, solution was found to contain 33% sucrose, not 25% as initially reported) or water prior to heel stick in sick infants who had a mean NTISS score ranging from 8.4 to 10.1 (n=128, 85 males, 43 females, mean gestational age approximately 36 wk, mean PNA 17-23 days); neonatal unit and cardiac unit settings	Outcome measures: 4-point subset of the NFCS, crying (duration of first cry, duration of crying during the procedure, and duration of crying during recovery), heart rate, and SpO <sub>2</sub>	Pain as indicated by the facial score was lower at heel lance ( $P=0.02$ ) and at 1 and 2 min postprocedure ( $P=0.04$ , $P=0.046$ ) in the sucrose group; there was no difference during heel squeeze and at the third min postprocedure, no difference in crying during the procedure, nor was there a difference in duration of first cry, but postprocedural crying was reduced in the sucrose group ( $P=0.01$ ); no difference in heart rate or oxygen saturation between the groups	No primary outcome measure defined; the outcome measures were compared at multiple time points without statistical correction; generalizability to ED patients is limited; this was a population of sick inpatients; more than 50% had surgery, more than 85% were receiving enteral feeds; pacifier use was at discretion of the treating nurse and was higher in the sucrose group; post hoc analysis did not identify this as a confounder; despite randomization, the placebo group was more ill, as per an illness severity score; post hoc regression analysis revealed that this may have led to an underestimation of the effect of sucrose; adverse events not reported	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Herschel et al <sup>136</sup>	1998	Randomized controlled trial	Compared 50% sucrose in a pacifier, dorsal penile nerve block, or control (no treatment) during circumcision in healthy, full-term, male newborns (n=119, mean gestational age 39 wk, mean PNA 24-27 h); general care nursery setting	Primary outcome measures: change in heart rate, and SpO <sub>2</sub> during the procedure and recovery; data loss due to movement was also compared	Elevation was greater throughout the procedure in the control group than in either treatment group ( $P<0.001$ ); mean changes in heart rate from baseline were 37 in the control group, 27 in the sucrose group, and 10 in the dorsal penile nerve block group ( $P<0.001$ ); no difference in SpO <sub>2</sub> among the groups; relative risk of data loss due to movement in the sucrose group compared with control was 0.26 (95% CI 0.18–0.36)	External validity limited by the fact that circumcision is not an ED procedure; only physiologic outcome measures were used, and there was difficulty in recording SpO <sub>2</sub> during procedure; no behavioral measures of pain were recorded; adverse events not reported	III
Mitchell et al <sup>137</sup>	2004	Randomized controlled trial	Compared 3 staggered doses of 0.1 cc of 24% sucrose or water by pacifier before and during eye examination for retinopathy of prematurity in very preterm infants; all infants received topical anesthetic and a pacifier (n=30, 7 males, 23 females, mean gestational age 26-27 wk, mean PNA 8 wk); NICU study	Outcome measure: PIPP score	The PIPP score was significantly reduced in the sucrose group only during the active eye examination phase (8.8 vs 11.4; $P=0.0077$ ) not during preparation (eye drop application) or recovery	Limited generalizability to ED setting because population was preterm, low-birth-weight infants undergoing a procedure that is not performed in the ED and is considered to be “severely invasive”	III
Mohan et al <sup>138</sup>	1998	Randomized controlled trial	Compared a pacifier containing 2 cc of 24% sucrose, EMLA cream, EMLA plus sucrose pacifier, vs a water-dipped pacifier for healthy, full-term males undergoing circumcision (n=80, gestational age 37-42 wk, PNA 1.6 to 2.3 days); well-baby nursery setting	Outcome measure: physiologic indicators (heart rate, blood pressure, SpO <sub>2</sub> ) and duration of crying/duration of procedure	SpO <sub>2</sub> for the sucrose group differed significantly from the water-pacifier group across all time points ( $P=0.03$ ); heart rate and blood pressure did not differ between the sucrose group and control; all treatment groups cried less than the “control” ( $P<0.01$ ); patients receiving EMLA and EMLA plus sucrose cried significantly less than the sucrose group ( $P<0.01$ )	External validity compromised, circumcision not an ED procedure; control group (pacifier with water) excluded from randomization process; unclear whether outcome assessment was blinded	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Ramenghi et al <sup>139</sup>	1996	Randomized controlled trial (crossover design)	Compared 1 cc of 25% sucrose vs water prior to heel stick in healthy, preterm infants (n=15 with each subject measured twice, median gestational age 33 wk, median PNA 2 days)	Outcome measures: duration of first cry, percentage cry over 5 min, heart rate, and changes in facial expressions on a 4-point scale	The duration of first cry was significantly shorter in the sucrose group (12 vs 23 seconds, $P=0.004$ ), as was the percentage cry over 5 mins (16.6 seconds vs 6 seconds, $P=0.018$ ); heart rate did not differ significantly; mean pain scores were lower in the sucrose group at 1 and 3 min poststimulus	Limited external validity, enrolled only premature infants; the facial expression scale outcome measure is of questionable reliability and validity; no adverse effects were seen	III
Rushforth and Levene <sup>140</sup>	1993	Randomized controlled trial	Compared 2 cc of 7.5% sucrose vs water prior to heel stick in full-term infants (n=52, 20 males, 32 females, median gestational age 38-39 wk, median PNA 6 days)	Outcome measure: duration of crying	There was no difference in crying between the groups	Dose was likely too low to show effect	III
Stang et al <sup>141</sup>	1997	Randomized controlled trial	During circumcision compared group I: a padded chair for circumcision, with a dorsal penile nerve block and a pacifier; group II: the standard restraint board, dorsal penile nerve block with buffered lidocaine, and a pacifier; group III: standard restraint board, dorsal penile nerve block, and a pacifier dipped in 24% sucrose; and group IV: standard restraint, dorsal penile nerve block, and a pacifier (n=80, 80 males, mean gestational age 39.5 wk, mean PNA 35.1 h); community hospital setting	Outcome measures: behavior as measured by the Brazelton Behavioral State Scale at time points throughout the procedure, and plasma cortisol measured 30 min after the procedure	The padded chair group and the sucrose pacifier group showed less behavioral distress overall than the other groups ( $P<0.05$ ); the sucrose group cried significantly less 2 min after the dorsal penile nerve block (0.003) and during the circumcision itself ( $P=0.002$ ); cortisol levels did not differ among groups	Lack of generalizability to the ED, circumcision is not an ED procedure; nonstandard outcome measure limits comparison with other studies	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Barr et al <sup>142</sup>	1995	Randomized controlled trial	Compared 0.75 cc of 50% sucrose vs water in healthy 2- and 4-mo-olds receiving intramuscular vaccinations (n=57, 31 males, 26 females); ambulatory pediatric clinic setting	Outcomes included: percentage of time crying (“audible negative vocalizations and facial grimace”) during and postinjection, relationship of age to response, and whether effect was on pain response during procedure or during recovery period	There was no difference in crying during the procedure, but sucrose significantly reduced postinjection crying compared with water (83% vs 69%, $P<0.05$ ); overall, crying was greater in younger than older infants, but there did not appear to be a difference in effectiveness of sucrose between the different age groups	Limited external validity, findings in this healthy outpatient population may not generalize to infants presenting to the ED; one of the few articles to assess sucrose in older infants	II
Lewindon et al <sup>143</sup>	1998	Randomized controlled trial	Compared 2 cc of 75% sucrose vs water in healthy infants born at >34 wk presenting for immunization at 2, 4, and 6 mo (n=107, 56 males, 51 females); outpatient clinic setting	Primary outcome measures: crying, duration of first cry, sum total crying, and start to finish crying; the Oucher Scale was used so that nurses and caregivers could subjectively assess infant distress	All measures of cry were shorter in the sucrose group, including duration of first cry (42 vs 29 seconds; $P<0.0003$ ), sum total crying (59 vs 36 seconds; $P<0.000008$ ), total crying time (69 vs 43 seconds; $P<0.00002$ ); nurses perceived a lower level of distress according to Oucher Scale in the sucrose group, but caregivers did not differ in their perception of infant distress	Unusually high dose of sucrose; subjective Oucher Scale was validated as a self-reporting pain scale for older children, not as it was used in this study; “usual” parental cuddling practice was observed for all neonates	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Reis et al <sup>144</sup>	2003	Randomized controlled trial	Infants undergoing intramuscular vaccinations (4 injections), comparing 25% sucrose from a bottle 2 min before the procedure with continued "oral stimulation" plus parental holding vs no intervention (n=116, 59 males, 57 females, mean age 9.5 wk); primary care center setting	Primary outcome measures: first cry and total cry duration from the beginning of the procedure; change from baseline to maximum heart rate was also assessed; secondary outcome measures: parental and nurse preference	First cry duration was 19 seconds in the sucrose group vs 58 seconds in the control group (95% CI for treatment effect -11 to -42); total cry duration was 92 seconds vs 188 seconds (95% CI for treatment effect -1 to -38); no difference in change in heart rate; parents preferred the intervention, as measured by a VAS; nurses showed no preference regarding ease of administration	Effect of sucrose could not be separated from the effect of the other interventions; parents and nurses who participated in providing the intervention could not be blinded to treatment group; investigators were blinded to audiotaped cry assessment, which was the primary outcome measure	III
Blass and Shah <sup>145</sup>	1995	Non-randomized controlled trial	2 distinct sections of study; the first section compared 2 cc of 0.17, 0.34, or 0.51 M sucrose, water, or no intervention given during 2 min prior to heel stick; second section looked at 0.34 M sucrose given 30, 60, 90, 120, and 240 seconds before heel stick; both enrolled healthy newborns, gestational age and PNA not specified (n=72, 46 males, 26 females); community hospital setting	Outcome measure: "% of crying per unit time" during procedure and for subsequent 3 min	Authors report "sucrose was an effective analgesic agent" ( $P<0.03$ ); from the figures, it appears that 0.34 M and 0.51 M sucrose was more effective than 0.17 M or water in reducing crying during heel stick, and there was no difference postprocedure, although $P$ values are not reported; infants who received the sucrose 120 seconds before heel stick cried significantly less than those who received the sucrose earlier or later	Essentially 2 studies: the first designed to elucidate dose-response curve and the second to define the temporal characteristics of antinociceptive effect of sucrose; number of infants assigned to control vs each treatment group not stated; total number in either component of the study not specified; protocol for treatment group selection was not specified	III

**Evidentiary Table (continued).**

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Coskun et al <sup>147</sup>	2001	Prospective observational study	360 patients age 2 wk to 8 y, undergoing echocardiography; 2 doses of chloral hydrate: age <2 y or with cyanotic heart disease 50-75 mg/kg, others 75-100 mg/kg	Efficacy determined by completion of study	Chloral hydrate successful sedation 95%; desaturation 3%; hypoxia in patients with genetic disorders but not cardiac problems	“23% refused oral drug because of bitter taste, 30% of the remaining patients vomited after oral drug administration; a significant decrease of oxygen saturation was recorded in half the patients with Down syndrome; failure of adequate sedation occurred in 71% (10/14) of patients with a genetic disorder (12 Down syndrome, 2 fragile x syndrome)”	Efficacy II Safety II
Wheeler et al <sup>148</sup>	2001	Randomized, controlled trial; blinded	40 children <5 y of age undergoing echocardiography; chloral hydrate 75 mg/kg vs midazolam 0.5 mg/kg	Objective scoring system for sedation; objective criteria for monitoring of vital signs	Chloral hydrate deep sedation 93% vs midazolam 36% ( $P=0.001$ ); no change in time to onset of sedation but chloral hydrate longer duration of action (37.4 min vs 80.6 min)	Echocardiography not common ED procedure	Efficacy I Safety II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Marti-Bonmati et al <sup>149</sup>	1995	Randomized, blinded, prospective dosage study	97 children received either 70 mg/kg or 100 mg/kg chloral hydrate for MRI imaging	Efficacy defined as successful completion of study with 95% of images free of motion artifact	Adequate sedation with initial dose of chloral hydrate in 64% of the 70 mg/kg group and 87% of the 100 mg/kg group ( $P<0.05$ ); additional doses of chloral hydrate brought groups up to 92% and 100% success; time to sedation was 28 min in lower-dose group and 21 min in higher-dose group ( $P<0.05$ ); time to awakening did not differ between dosage groups; adverse events, including vomiting and nervousness in 21% of patients, but not statistically different between dosage groups; no cardiorespiratory depression	Age, weight, and diagnosis influenced efficacy; “older and heavier children and those with white matter disease are more likely not to be satisfactorily sedated”	Efficacy I  Safety I

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Malviya et al <sup>150</sup>	2004	Randomized, blinded, controlled trial	70 children randomized to chloral hydrate 75 mg/kg or pentobarbital 2-5 mg/kg intravenous; patients could be supplemented with intravenous midazolam	Formalized grading system for quality of MRI studies and sedation scores	Sedation scores significantly higher for pentobarbital ( $P<0.01$ ); time to onset shorter for pentobarbital ( $P=0.001$ ) but time to discharge was similar for 2 groups; in chloral hydrate group 37% required intravenous midazolam compared to 9% of pentobarbital group; sedation success was 97% for chloral hydrate and 91% for pentobarbital ( $P=NS$ ); desaturation in 11% of chloral hydrate and 17% of pentobarbital ( $P=NS$ ); major motion artifact in 4% chloral hydrate; postdischarge h until return to baseline 11 for chloral hydrate, 17 for pentobarbital ( $P<0.05$ )		Efficacy I  Safety I
D'Agostino and Terndrup <sup>151</sup>	2000	Randomized, controlled, blinded study	33 children aged 0-93 mo sedated for outpatient imaging study received either chloral hydrate 75 mg/kg or midazolam 0.5 mg/kg	Efficacy determined by completion of study	Adequate sedation in 100% chloral hydrate compared to 50% midazolam ( $P<0.05$ ); need for supplemental medication 9% of chloral hydrate group and 55% of midazolam group ( $P<0.05$ ); duration of sedation not statistically different: 95 min for chloral hydrate vs 76 min for midazolam		Efficacy I  Safety I

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Thompson et al <sup>152</sup>	1982	Randomized, controlled trial	582 patients randomized to chloral hydrate 80 mg/kg, AMPS, or general anesthesia with endotracheal intubation for CT study	Sedation defined by successful completion of CT without motion artifact	Failure 15% for chloral hydrate, 12% for AMPS; complications not reported for each group but 3.5% overall	No objective standards for efficacy; no data on chloral hydrate safety	Efficacy II Safety N/A
Ronchera-Oms et al <sup>153</sup>	1994	Nonrandomized, observational study	596 elective MRI patients; chloral hydrate dose not specified	Efficacy determined by quality of MRI and motion artifacts	Mean dose 64 mg/kg; 76.2% successful after first dose, 94.1% successful after total dose; 9.9% adverse reactions; nausea and vomiting most common; more frequent in older children	“15% failure rate in older children (>7 y), <5% failure rate in younger children (<36 mo); effectiveness around 80% in children with encephalic white matter alterations, medullary tumors/syringohydromyelia”	Efficacy II Safety II
Greenberg et al <sup>154</sup>	1993	Prospective, observational study	300 children ages 1 mo to 11 y, who received 100 mg/kg chloral hydrate for MRI; efficacy and safety correlated by age	Efficacy by completion of study	Efficacy: 91% completed MRI overall, children <48 mo 96%, children 4-11 y 81%; failure rate increased proportionately with increasing age from 2% in infants to 26% in children 6-11 y ( $P<0.0005$ ); respiratory depression more common in children <24 mo (6.7%) ( $P=0.05$ )	“Success rate=96% (age ≤48 mo) versus 81% for age >48 mo”	Efficacy II Safety II

**Evidentiary Table (continued).**

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
McCarver-May et al <sup>155</sup>	1996	Randomized, blinded, crossover study	7 term neonates undergoing CT and single photon emission CT 2 days apart; chloral hydrate (75 mg/kg) given for first study, midazolam (0.2 mg/kg) for second study; all infants had meconium aspiration syndrome and persistent pulmonary hypertension	Specific sedation definitions used	All infants fell asleep with single dose of chloral hydrate compared with only 42% of midazolam infants; 57% of infants in both groups desaturated	Small number of unique patients	Efficacy II Safety III
Pereira et al <sup>156</sup>	1993	Retrospective examination of prospectively collected data	2,178 patients; ages newborn to 17 y; sedation for outpatient CT imaging; options included chloral hydrate 50-80 mg with option for supplemental dose of 25-40 mg/kg, intravenous pentobarbital (2.5 mg/kg, 1.25 mg/kg, 1.25 mg/kg protocol), intramuscular pentobarbital (5-6 mg/kg), or meperidine, chlorpromazine, and promethazine (CM-3)	Efficacy defined by scoring system based on quality of images	Good or adequate studies were obtained in 96.4% of chloral hydrate patients, 97.7% of intramuscular pentobarbital, 96.9% of intravenous pentobarbital, and 70.7% of CM-3 patients; duration including induction time was 92 min for chloral hydrate, 115 min for intramuscular pentobarbital, 63 min for intravenous pentobarbital, and 111 min for CM-3 patients ( $P<0.001$ )		Efficacy II Safety II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Lipshitz et al <sup>157</sup>	1993	Prospective, observational study	140 children, 0-36 mo undergoing echocardiography; mean dose chloral hydrate 87 mg/kg; objective to evaluate effects of age, food, and nap schedule on chloral hydrate sedation; follow-up parental survey at 24 h	Side effects (ataxia, excitement), delayed sedation, light sleep, behavioral changes were assessed	No increase in hypoxia in children cyanotic at baseline; beginning and sedated saturations highly correlated ( $P<0.0001$ ); effect of delivery of medication increased when timing procedure with nap time; paradoxical excitement in 18%, 3 children never fell asleep; variables associated with paradoxical excitement and/or ataxia were older age ( $P<.001$ ) and had a higher total dose ( $P=0.0003$ ), successful sedation=97.9%	No objective efficacy criteria	Efficacy II Safety II
Malviya et al <sup>158</sup>	2000	Retrospective examination of prospectively collected data	922 children ages birth to 18 y sedated for CT or MRI were compared with 140 children undergoing the same studies under general anesthesia	Quality of diagnostic scans was evaluated as adequacy of sedation	Chloral hydrate was 96% effective in permitting completion of scans compared to 91% for benzodiazepine ( $P<0.02$ ); mean dose of chloral hydrate was 60.1 mg/kg; oxygen desaturation in 3% of chloral hydrate patients, and 1% required airway interventions	Did not report specifics of chloral hydrate vs other agents	Efficacy II Safety II

**Evidentiary Table (continued).**

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Hubbard et al <sup>159</sup>	1992	Observational study	407 outpatients (aged 1 day to 18 y) sedated for CT or MRI, 265 received chloral hydrate (mean dose 80 mg/kg), 25% required a second dose of chloral hydrate; 115 received nembutal, 27 patients received other sedatives		Of the 34 patients who had transient oxygen saturation decrease, 49% had some “disease that compromised their airway,” including rhinitis, sinusitis, mandibular hypoplasia, Down syndrome, and obesity; certain patients were difficult to sedate; these were children with mental retardation, patients receiving chemotherapy, and patients habituated to sedation; patients on antiseizure medication required higher sedation doses; successful chloral hydrate sedation=98%	They did not separate the various sedations and complications/failed sedations, although the majority (65%) of patients received chloral hydrate	Efficacy III Safety III
Rumm et al <sup>160</sup>	1990	Prospective, observational study	50 children undergoing diagnostic study (CT, MRI, EEG, bone scan, other); mean initial dose=58 mg/kg	Effective sedation defined by successful completion of diagnostic test with a sedation score of at least 3 of 4 on 4-point scale at completion of test	Single dose success rate=86%; no complications or side effects in any patients, although 2 of the 7 “failures” of sedation “vomited a considerable portion of their initial dose”	Children with neurologic disorders had a much greater (27% vs 4%) failure rate than “normal” children; no complications or side effects, yet note 2 of 7 failures vomited their medication	Efficacy III Safety III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Seiler et al <sup>161</sup>	2001	Observational study	Children undergoing radiation therapy for cancer, age 9 mo to 9 y; 148 sedations were done; dose 75-100 mg/kg by mouth or per rectal initially, repeat 25 mg/kg dose if lower 75 mg/kg dose was used initially up to a maximum of 2 g; mean dose 100 mg/kg (range 10-167 mg/kg); chloral hydrate was used in 30 procedures, midazolam in 78, meperidine in 15, other sedatives in 25		Satisfactory sedation for treatment: chloral hydrate 60%, meperidine 60%, midazolam 82%; unable to treat: chloral hydrate 20%, meperidine 13%, midazolam 5%; no serious complications; "chloral hydrate was the least successful with at least 1 complication occurring in 23% (7/30)," vomiting 13% (4/30), pulse >160 beats/min 10% (3/30)	Small number; high ECOG status III or IV, selected patient population (sick cancer patients)	Efficacy III Safety III
Rooks et al <sup>162</sup>	2003	Nonrandomized, observational study	Review of prospectively collected data on 675 infants who received oral pentobarbital (initial dose 4 mg/kg) or chloral hydrate (50 mg/kg) for radiology studies (MRI, CT, other)	Efficacy determined by completion of study	Efficacy 99.7%; adverse events pentobarbital 1.6%, chloral hydrate 1.7%	No formalized scoring system for efficacy; non-randomized	Efficacy III Safety III
Mason et al <sup>163</sup>	2004	Retrospective review of prospectively collected data	1,316 infants <1 y receiving oral sedation for radiology imaging studies; chloral hydrate dose 50 mg/kg, pentobarbital 4 mg/kg	Efficacy defined as successful completion of study	Time to sedation (17-18 min) and discharge similar (102-103 min); success rate for chloral hydrate was 98.7% and for pentobarbital was 99.5% ( $P=NS$ ); complications including hypoxia more common in chloral hydrate group (2.7%) vs pentobarbital group (0.5%) ( $P=0.01$ )	No formalized scoring system	Efficacy III Safety III

**Evidentiary Table (continued).**

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Chung et al <sup>164</sup>	2000	Prospective observational study	54 infants ages 2-13 mo, undergoing radiology imaging studies received either chloral hydrate (50-100 mg/kg) or pentobarbital (4-6 mg/kg) orally; fasted 4.8 h; mean time to onset 19 min (+/- 13); time to discharge 102 (+/- 33)	Efficacy defined by ability to complete test	Sedation success 100% for chloral hydrate and 90% for the pentobarbital group; infants were more likely to accept pentobarbital than chloral hydrate ( $P<0.001$ ); no desaturation reported	Parents selected sedative agent	Efficacy III Safety III
Vade et al <sup>165</sup>	1995	Prospective observational study	410 children undergoing imaging study received chloral hydrate in age-based dosing regimen; age <1 y received 50 mg/kg, age 1-4 y received 75 mg/kg plus hydroxyzine (0.8 mg/kg)	Efficacy defined as successful completion of study with 95% of images free of motion artifact	Successful sedation in 99.5% of patients; prolonged sedation 3% of chloral hydrate only group but 17% of chloral hydrate plus hydroxyzine group; mild hypoxia in 9% of chloral hydrate only group and 5% of combined group; moderate-to-severe hypoxia with oxygen desaturation, <90% occurred in 0.5% of groups		Efficacy III Safety III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Napoli et al <sup>166</sup>	1996	Prospective observational study	405 children ages 3 weeks to 14 y received chloral hydrate (50-100 mg/kg) for echocardiography	Efficacy by completion of study	Successful sedation 98%; time to sedation 30 min or less in 82%, 30-60 min in 12%, and >60 min in 4%; oxygen saturation decreased by >5% in 6% of patients and was treated with head repositioning in 83% and supplemental oxygen in the remainder; oxygen desaturation more likely in children with genetic syndromes	“Children ≤3 y 99% successful sedation, >3 y 84% successful sedation ( $P=0.003$ )”; decreases in oxygen saturation occurred more commonly in children with trisomy 21 (7/13=53.8%) than in children without genetic syndromes (17/384=4.4%); “chloral hydrate is a safe and effective agent for sedation of children with congenital heart disease including cyanotic heart disease”	Efficacy III Safety III
Lichenstein et al <sup>167</sup>	1993	Retrospective chart review	424 patients in a pediatric ED undergoing procedural sedation using chloral hydrate; mean initial dose 51 mg/kg; age range 0.4 to 209 mo, 55% male, 61% African American	Successful sedation not defined; sedation was for diagnostic or minor surgical procedures	Overall 82% first dose, 88% total dose success rate; no adverse effects other than vomiting and hyperexcitability; success rate (first dose, second dose, total) by age was: 0-0.9 y 98%, 100%, 100%; 1.0-1.9 y 84%, 91%, 97%; 2.0-2.9 y 76%, 87%, 97%; 3 y 76%, 85%, 89%; chloral hydrate as a single agent safe without life-threatening reactions	Retrospective chart review; no standardized scoring for efficacy or safety; specific procedures not defined	Efficacy III Safety III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Weir et al <sup>168</sup>	1986	Prospective, randomized trial	252 children undergoing sedation for CT (107), EEG (67), other (78); randomized to one of 3 sedation regimens: chloral hydrate (N=82) by mouth, DPT (N=113) intramuscular, or DN (N=57) intramuscular; initial doses: chloral hydrate 30 mg/kg; DPT=demerol 2 mg/kg up to 50 mg maximum, phenergan, thorazine; DN=demerol 50 mg/M2 up to 50 mg maximum, nembital 90 mg/M2 up to 90 mg maximum; repeat doses as needed were: chloral hydrate 15 mg/kg for failure of chloral hydrate or DPT, and nembital titrated slowly intravenously for failure of DN	Success was defined as procedure performed; complications were those that required hospitalization	Success rates: chloral hydrate 80%, DPT 86%, DN 86% ( <i>P</i> =NS); failure rates for chloral hydrate were greater in the older patients (>3 y); most failures tended to occur in children with seizure disorders or retardation and required augmentation more frequently than patients without these conditions; the highest failure rates occurred with CT scans and EEGs; other is surgical examinations or procedures (urologic, otolaryngologic, orthopedic, ophthalmologic, dental), nuclear scans and radiologic procedures; no patient experienced an adverse reaction that resulted in hospitalization	Limitations: dosages of all drugs not given; some patients not randomized if surgeon had a preference for a sedative regimen	Efficacy III Safety III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Sanborn et al <sup>169</sup>	2005	Observational study	16,647 sedations in 13,408 pediatric patients (mean age 4.8 y); 645 chloral hydrate (per mouth or per rectal); 9,052 intravenous pentobarbital, 2,183 pentobarbital per mouth, 772 intravenous pentobarbital+fentanyl, 606 intravenous pentobarbital+fentanyl+midazolam, 1,260 intravenous midazolam+fentanyl, 229 other chloral hydrate; dose 20-50 mg/kg, repeat every 30 min up to maximum 100 mg/kg or 2 q; patients 95% ASA status I or II; radiology imaging		Adverse events rates: 1.8% intravenous pentobarbital+fentanyl, 1.2% chloral hydrate by mouth, 1.2% intravenous pentobarbital+fentanyl+midazolam, 1% intravenous pentobarbital+midazolam, 0.2% intravenous pentobarbital, 0.1% pentobarbital by mouth; adverse respiratory event rate was higher for chloral hydrate than pentobarbital by mouth or intravenous ( $P<.001$ ); of 70 patients (0.4%) with adverse respiratory events 20 (29%) had a history of serious respiratory disease (asthma, bronchiolitis, pneumonia, congenital cystic adenomatoid malformation) (N=12); there were no aspirations with chloral hydrate (1 with IV pentobarbital+fentanyl+midazolam, 1 with IV pentobarbital); only 1.1% (7/645) desaturations, 0.1% (1/645) needed airway resuscitation; all airway resuscitations were brief, with the patient receiving oxygen positive pressure ventilation with a face mask	Patient characteristics for each sedative regimen were not given	Efficacy III Safety III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Kao et al <sup>170</sup>	1999	Prospective telephone interview; consecutive cohort of children	80 children ages 2 mo to 11 y sedated with chloral hydrate (80 mg/kg) for radiology imaging study (CT or MRI); supplemental dosing permitted	Telephone survey on day after procedure	Normal activities were resumed at 2 h in 24%, 2-4 h in 22%, 4-8 h in 24%, and >8 h or overnight in 30% of patients; unsteadiness in 68%, hyperactivity in 29%	Survey the next day may limit accuracy of time estimates; no description of the decision process/procedure for discharge; most ASA class I or II, but 7 ASA class III, and 2 ASA class IV; 67% (80 of 119) response rate	Chloral hydrate Efficacy N/A Safety III  Discharge III
Reeves et al <sup>174</sup>	1996	Randomized controlled trial; blinded	40 children sedated for dental procedures with either chloral hydrate (50 mg/kg) plus hydroxyzine (25 mg) or midazolam (0.5 mg/kg) plus acetaminophen (10 mg/kg); given orally	Sedation defined by objective scale by trained observers with excellent interrater reliability	Chloral hydrate group demonstrated better somnolence at time of procedure ( $P=0.002$ )	No safety data; efficacy data determined by sedation scale; no efficacy data related to performance of procedure	Efficacy II  Safety N/A
Malviya et al <sup>175</sup>	2000	Prospective observational study	376 children had telephone interviews 1 day after sedation for imaging study; medication selected by radiologists	Formalized patient family survey used to collect information	Motor imbalance was noted in 31% of chloral hydrate group compared to 18% of midazolam group ( $P<0.05$ ); agitation in 18% of the pure chloral hydrate group compared to 8% of midazolam group ( $P=NS$ ); 3 children in chloral hydrate group returned to ED for prolonged sedation; only 48% of both the chloral hydrate and midazolam groups returned to baseline activity within 8 h, although 89% were at baseline at 24 h	Clinical significance of survey questions not indicated	Efficacy N/A  Safety III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Malviya et al <sup>197</sup>	2004	Clinical trial	Interobserver agreement between clinical scores and the Bispectral Index	Comparison of the University of Michigan Sedation Scale score, the Modified Maintenance of Wakefulness Test, and the Bispectral Index (criterion standard)	Based on a criterion standard of a BIS value $\geq 90$ as indicative of discharge readiness, a University of Michigan Sedation Scale score of 0 or 1 had a sensitivity of 89%, a specificity of 87%, and a positive predictive value of 70%; a Modified Maintenance of Wakefulness Test using 20 min as the standard had a sensitivity of 77%, a specificity of 89%, and a positive predictive value of 89%	Small sample size with only 29 children; all ASA class III undergoing echocardiogram; 27 received chloral hydrate, 2 received midazolam; the same individual recording the University of Michigan Sedation Scale also scored the Modified Maintenance of Wakefulness Test (potential for bias); institutional discharge guidelines were used relying on the University of Michigan Sedation Scale; criterion standard for discharge readiness defined as BIS value $\geq 90$ (? validated); no follow-up after discharge	III
Mason et al <sup>198</sup>	2004	Retrospective medical record review with an uncontrolled comparison (observational)	Reviewed records from a sedation database at a single institution	Description of time to discharge, duration of sedation, sedation failure rate	Mean time to discharge was similar in the oral and intravenous groups (108 min vs 109 min)	All infants younger than 12 mo; all received pentobarbital; comparison is uncontrolled (potential for bias); large sample size (2,164 infants); used predefined discharge criteria (not validated)	III

**Evidentiary Table (continued).**

<b>Study</b>	<b>Year</b>	<b>Design</b>	<b>Intervention(s)/Test(s)/Modality</b>	<b>Outcome Measure/Criterion Standard</b>	<b>Results</b>	<b>Limitations/Comments</b>	<b>Class</b>
Malviya et al <sup>201</sup>	2002	Prospective study (selection process not clear)	Real time assessment and a review of videotaped segments of sedations on children undergoing sedation for CT scanning	Interobserver reliability for the University of Michigan Sedation Scale for videotaped segments; criterion standard was the Observer's Assessment of Alertness/Sedation Scale; comparison was also made with a nurse recording a visual analogue scale	There was good agreement at lighter sedation levels (University of Michigan Sedation Scale scores of 0 and 1) but less agreement at higher sedation scores (University of Michigan Sedation Scale scores of 2 and 3); there was poor agreement at the time of discharge	Small sample size with only 32 children in the study; selection criteria for inclusion in the study are not clearly presented; all children were ASA class I or II; children were 4 mo to 5 y of age; all children received chloral hydrate	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Newman et al <sup>205</sup>	2003	Database review (retrospective review of a prospectively generated database)	Description of adverse events and their timing in relation to the timing of a sedation; database included information from 24-h follow-up telephone calls	Description of the timing of "serious" and "other" adverse effects	Most (92%) adverse effects occurred during the procedure (only 8% after); of 1,341 sedations, 159 serious adverse effects were identified; serious adverse effects that occurred more than 25 min after the final sedation medication administration occurred in children who had also experienced adverse effects earlier; authors concluded it is safe to discharge approximately 30 min after final sedation administration if no adverse effects have occurred	Multiple drugs were administered alone and in a variety of combinations; several different routes for drug administration were used; telephone follow-up to evaluate for late complications was available for only 64%; interobserver reliability was assessed for 10% of records with a simple concordance rate (85% agreement for the nature of adverse events and 85% for times recorded)	III

*AAP*, American Academy of Pediatrics; *AMPS*, atropine, meperidine, promethazine, and secobarbital; *ANCOVA*, analysis of covariance; *ASA*, American Society of Anesthesiologists; *BIS*, bispectral index; *CHEOPS*, Children's Hospital of Eastern Ontario Pain Scale; *CI*, confidence interval; *CNS*, central nervous system; *CT*, computed tomography; *CO<sub>2</sub>*, carbon dioxide; *DAN*, Douleur Aigue chez le Nouveau-ne; *ECG*, electrocardiogram; *ECOG*, Eastern Cooperative Oncology Group; *ED*, emergency department; *EEG*, electroencephalogram; *ETCO<sub>2</sub>*, end-tidal carbon dioxide; *FIO<sub>2</sub>*, fractional inspiratory oxygen; *FLACC*, Face, Leg, Activity, Crying, Consolability; *g*, gram; *GERD*, gastroesophageal reflux disease; *h*, hour; *IQR*, interquartile range; *M*, moles per liter of solution; *min*, minute; *mo*, month; *MRI*, magnetic resonance imaging; *N<sub>2</sub>*, nitrogen; *N<sub>2</sub>O*, nitrous oxide; *N/A*, not applicable; *NEFA*, nonesterified fatty acid; *NFCS*, Neonatal Facial Coding System; *NICU*, neonatal intensive care unit; *NPO*, nothing by mouth; *NS*, not significant; *NTISS*, Neonatal Therapeutic Intervention Scoring System; *OR*, odds ratio; *OSBD-R*, Observational Scale of Behavioral Distress-Revised; *PCA*, postconceptional age; *PIPP*, Premature Infant Pain Profile; *PNA*, postnatal age; *RN*, registered nurse; *SaO<sub>2</sub>*, arterial blood oxygen saturation; *SNAP-PE*, Scale for Neonatal Acute Physiology-Perinatal Extension; *SpO<sub>2</sub>*, pulse oximetry; *VAS*, visual analog scale; *vs*, versus; *wk*, week; *WMD*, weighted mean difference; *y*, year.