Challenges in paediatric procedural sedation: political, economic, and clinical aspects

K. P. Mason

Department of Anaesthesia, Harvard Medical School, Boston Children’s Hospital, Boston, MA, USA

E-mail: keira.mason@childrens.harvard.edu

Summary. Paediatric sedation has expanded in volume and demand over the past decade. In parallel with the increasing demand for and delivery of sedation by multi-specialty providers, conflicting political agendas have surfaced. With a limited selection of sedatives and few new sedatives to market over the past decade, some providers utilize agents that formerly were considered exclusive for administration by anaesthesiologists. This review highlights the important contributions to paediatric sedation over the past century. Considerations include the barriers and politics that impede progress and also future advances and contributions that may lie ahead.

Keywords: paediatric anaesthesia; safety; sedation

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Paediatric sedation has expanded, over the past decade, in volume and demand. It is now being delivered by specialists of anaesthesia, emergency medicine, dentistry, gastroenterology, intensive care, paediatrics, pulmonology, cardiology, neurology, and nursing. In parallel with the increasing demand for and delivery of sedation by multi-specialty providers, conflicting political agendas have surfaced. With a limited selection of sedatives and few new sedatives to market over the past decade, some providers utilize agents that formerly were considered exclusive for administration by anaesthesiologists. Worldwide there is not consistent agreement on sedation practice and delivery. In some countries, government has interceded to regulate sedation delivery and reimbursement. For example, in the USA, deep sedation by registered nurses is no longer reimbursed under the Center for Medicaid and Medicare Services (CMS). Some specialty societies, notably those of emergency medicine, dentistry, anaesthesia, gastroenterology, and paediatric, have published their own sedation guidelines, recommendations, policies, and statements for the practice of sedation.

The global challenge is the paucity of large, prospective, collaborative outcome studies. Without these studies, sedation providers are unable to determine which sedation practices are optimal for favourable outcomes. It may not be practical or realistic to standardize guidelines between different specialties. However, there are contradictions even within the same specialty: specialty guidelines, recommendations and statements can be inconsistent between countries within the same continent. For example, in Europe there is disagreement between some countries on whether propofol should be restricted to delivery by anaesthesiologists. To advance the field of paediatric sedation over the next century, this author believes that large, multi-centre randomized controlled trials must be designed to guide optimal sedation practice, recognizing that sedation practice cannot always be the same between specialties. There are a range of topics that must be examined: provider skillset, credentialing, the role of simulation in training and maintaining proficiency, physiological monitoring, routes and methods of delivery, and the design and interpretation of clinical studies.

Of foremost importance, we need to determine the best method of acquiring and maintaining sedation training and credentialing. This task is not straightforward because there are unresolved questions. Should the criteria for sedation competence differ between specialists (e.g. dental vs gastroenterology), sedatives (e.g. propofol vs dexmedetomidine), or targeted depth of sedation (e.g. moderate vs deep)? Many such questions must be considered when developing a training and sedation credentialing programme for sedation.

Although there may be agreement on the undeniably necessary skills (establishing positive pressure ventilation, recognizing airway obstruction, etc.), there is no consensus on how to
acquire and demonstrate proficiency. For example, the ability to establish effective mask ventilation and positive pressure ventilation is critical. Unanswered, however, is how these skills should be acquired, demonstrated and maintained. Should the proficiency of these skills be tailored to institution, specialty or socioeconomic setting? For example, in developing countries, the Mapleson A circuit may be the most appropriate equipment for administering positive pressure ventilation. There remain other unanswered questions: is the ability to perform tracheal intubation necessary in order to deliver deep sedation? Should all sedation providers be able to demonstrate competence in laryngeal mask airway (LMA) placement? If yes, how many tracheal intubations or LMA placements should a provider perform in order to be able to achieve acceptable competence? Should the ability to intubate children of different age ranges be demonstrated, especially considering that there is a notable difference in airway anatomy (cephalad and anterior larynx with large, floppy epiglottis in newborns) between some age groups? If yes, how many infants must be intubated in order to exhibit competence? Should there be ongoing requirements to perform a minimum number of intubations annually? With the recent emphasis on the use of capnography, should providers need to demonstrate an understanding and competence in evaluating capnogram traces?

This review highlights important contributions to paediatric sedation over the past century and considers the barriers and politics that impede advancement and also the future advances and contributions that may lie ahead.

The past century in review: sedatives and their politics

Many of the sedatives used today were first described over a century ago. In a retrospective review, drug overdose, drug interactions, and administration of three or more sedatives were major contributors to critical incidents (death or permanent neurological injury). Overall, the majority of sedatives are used off-label in the paediatric population. Recently, the availability and utilization of some sedatives have been affected not only by their side effect profile, but also by politics and economics.

Chloral hydrate

The first synthetic sedative-hypnotic, was discovered in 1832 and described as a ‘neues hypnoticum und anaestheticum’ (new hypnotic and anaesthetic) in 1869. Administered to children as early as 1893, chloral hydrate over a century later, remains the foundation of sedation for dental, neurological (electroencephalograms), radiological (magnetic resonance imaging, computerized tomography), intensive care and cardiac imaging (echocardiography) procedures worldwide. In the USA, the pharmaceutical producer of chloral hydrate will cease its manufacture. Some individual pharmacies and institutions have responded by compounding (creation of particular pharmaceutical product to fit the unique needs of a patient) the chloral hydrate formulation. The economic effect of this production model has yet to be determined.25

Pentobarbital

Pentobarbital, known by the brand name Nembutal, was first administered in the 1930s. As early as 1965, the use of pentobarbital was described for paediatric sedation. Despite its long half-life of up to 48 h, it has a high safety profile that continues to favour pentobarbital administration worldwide for sedation delivery, particularly by non-anaesthesiologists. Utilized predominantly by the i.v. route, only one company is approved by the Food and Drug Administration (FDA) to distribute the injectable form in the USA. Manufactured by a Danish pharmaceutical company, Lundbeck, pentobarbital has recently gained worldwide notoriety as being the drug administered in the USA for death by lethal injection. After legislation by the European Union banning export of medications intended for death by lethal injection, Lundbeck threatened to halt its distribution to the USA when intended for such purposes. Although both chloral hydrate and pentobarbital lack analgesic properties, their predictable and low rate of adverse events, respiratory depression, and failed sedation continue to favour their use. In public opinion, however, pentobarbital conjures negative and risky connotations.

Propofol

Propofol, or 2,6-diisopropylphenol, was first used clinically as an anaesthetic in 1977. Propofol is an example of a medication that has fuelled the debate on which medications are appropriate for administration by non-anaesthesiologists. In June 2005, the American College of Gastroenterologists submitted a petition which was ultimately denied by the FDA to remove the warning that propofol be administered only by persons trained in the administration of general anaesthesia. At the time, less than a decade ago, this petition evoked emotionally charged arguments, both in defence and opposition, with the ultimate success of the American Society of Anesthesiologists (ASA) in their November 2005 testimony before the FDA to deny this request.

The current package insert limits propofol administration to persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure… (while) continuously monitored (patients) for early signs of hypotension, apnoea, airway obstruction, oxygen desaturation, or all. Promoting unconsciousness, propofol inhibits release of the arousal-promoting histamine neurotransmitter in the cerebral cortex. Similar to pentobarbital, propofol also attracted public attention when it was intended for death by lethal injection. A public outcry lead the European Union in 2000 to threaten a ban on exportation of propofol to the USA should it be used for capital punishment, torture or other cruel, inhuman or degrading treatment, or punishment. Propofol’s association with the death penalty and its association with the death of the well-known music idol Michael Jackson, have created a negative stigma in the public eye.
Fospropofol
Fospropofol is an alkylphenol-derived soluble prodrug of propofol, intended to offer benefits of reduced pain on injection, less risk of bacterial contamination, a larger therapeutic window with greater respiratory stability and a short terminal phase elimination half-life ($t_1/2$) of $\sim 0.8$ h.\textsuperscript{41} \textsuperscript{42} FDA approved in 2008 for Monitored Anaesthesia Care, fospropofol remains without paediatric labelling. To date, the majority of published experience has been limited to gastrointestinal endoscopies for adults, but also includes dental procedures and bronchoscopies.\textsuperscript{43} \textsuperscript{45} Despite a lack of significant adverse respiratory events, fospropofol’s side-effect profile of transient paresthesias in up to 69% and pruritus in up to 26% has limited its adoption as a sedative.\textsuperscript{46} \textsuperscript{47}

Ketamine
Ketamine was first approved in 1970 in the USA and is commonly administered by emergency medicine physicians for painful procedures, particularly in the paediatric population. First described in their literature in 1979, practice guidelines for ketamine administration have been published by the American College of Emergency Physician (ACEP).\textsuperscript{48} \textsuperscript{52} Worldwide it remains a commonly administered and essential medication, even recognized by the World Health Organization on their List of Essential Medicines for Children.\textsuperscript{53}

Etomidate
Etomidate was FDA approved for adults in 1982 and remains without paediatric labelling. Etomidate is associated with comparatively less hypotension and cardiovascular depression than occurs with most other sedatives and offers the advantage of rapid onset with a short elimination $t_1/2$ of 2.6 h.\textsuperscript{54} \textsuperscript{55} Without analgesic properties, etomidate has been used for procedural sedation (often in combination with opioids), most commonly by emergency medicine physicians who do not have access to propofol for diagnostic imaging and brief procedures such as cardioversion, closed reduction of orthopaedic injuries, and abscess incision and drainage.\textsuperscript{56} Over the past decade, it has fallen into disfavour, both for adults and children, because of reports of increased mortality with continuous infusions and adrenal suppression with a subsequent decrease (for a minimum of 24 h) in plasma cortisol.\textsuperscript{57} \textsuperscript{62}

Dexmedetomidine
Dexmedetomidine was approved in the USA in 1999 and in Europe in 2011 for sedation of adults in the intensive care unit. Dosing recommendations differ between the USA and Europe.\textsuperscript{63} \textsuperscript{64} A highly specific alpha-2 adrenergic agonist, dexmedetomidine is unique because it preserves respiratory function and simulates natural non-rapid eye movement (non-REM) sleep which has also led to its utilization as a sedative for electroencephalography.\textsuperscript{65} \textsuperscript{70} Dexmedetomidine should be avoided in patients on digoxin as there is an association between this combination and cardiac arrest and severe bradycardia.\textsuperscript{63} \textsuperscript{71} Its off-label use for paediatric sedation has mostly been for radiological imaging.\textsuperscript{3} \textsuperscript{32} \textsuperscript{35} \textsuperscript{72} \textsuperscript{80} As a sole sedative in non-intubated children, higher than ‘recommended’ (package insert) doses of dexmedetomidine must be delivered with anticipation of possible haemodynamic shifts (arterial pressure, heart rate) and cardiovascular effects (change in stroke index, cardiac index, systemic vascular resistance).\textsuperscript{77} \textsuperscript{78} \textsuperscript{81} \textsuperscript{82}

Sedation delivery politics, economics, policies, procedures, guidelines, and statements
This review highlights the evolution of sedation in the USA, as the American Society of Anesthesiologists, American College of Emergency Physicians, American College of Gastroenterologists, Joint Commission, FDA and Center for Medicaid and Medicare services have been the most visible and prolific in their responses and contributions to evolving sedation practices. Historically, dentists, neurologists and anaesthesiologists have been providing procedural sedation for paediatric patients since the 1960s.\textsuperscript{83} \textsuperscript{88} Emergency medicine physicians began delivering sedation in the 1970s.\textsuperscript{61} In the 1990s, as more procedures began to be performed in areas outside of the operating theatre, sedation delivery expanded to other specialists—paediatricians, neurologists, hospitalists, pulmonologists, and nurses. As sedation has evolved over the decades, the specialty societies have created and updated guidelines, policies and statements intended not only to guide their own practice, but in some cases, the practice of others outside their specialty. One example of this is the ASA which published its first guidelines addressing the delivery of sedation by non-anesthesia care providers in 1996. The ASA has subsequently presented updates, standards and statements on moderate and deep sedation, and on propofol delivery.\textsuperscript{89} \textsuperscript{94} The definition of deep sedation in the USA and Europe are similar: a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated or painful stimulation.\textsuperscript{95} \textsuperscript{96}

Apart from the ASA, other specialty (professional) societies have created guidelines for application by members of their own societies. In paediatrics, this began in the USA in 1983. Responding to the death of three children in a single dental office, the American Academy of Pediatrics published the first (with subsequent updates) guidelines for the sedation of children.\textsuperscript{97} \textsuperscript{102} The American College of Emergency Physicians, American Academy of Pediatric Dentistry (AAPD), American Dental Association, and American College of Gastrointestinal Endoscopy have independently published guidelines, some of which are evidence-based, to direct paediatric sedation by their members. Collectively, these guidelines span the breadth of sedation practice from pre-sedation assessment, the medical condition of the child, sedation environs, physiological monitoring, and recovery.\textsuperscript{7} \textsuperscript{8} \textsuperscript{14} \textsuperscript{100} \textsuperscript{103} \textsuperscript{112}

In the USA, the government is also involved through its CMS. This government involvement, by affecting the reimbursement of sedation, has had significant ramifications on sedation delivery. As early as 2004, the Joint Commission intended to
set the standard for sedation in any setting, when it first published (updated recently) a Comprehensive Accreditation Manual for Hospitals. In May 2010 (subsequently updated again in 2010 and 2011), the CMS had a significant impact on the delivery of sedation in the USA when it restricted reimbursement for deep sedation services to specific specialties. Appendix A of Revised Hospital Anesthesia Services Interpretive Guidelines—State Operations Manual limited administration of deep sedation to a qualified anaesthesiologist, a doctor of medicine or osteopathy (other than an anaesthesiologist), a dentist, oral surgeon, or podiatrist who is qualified to administer anaesthesia under State law, a certified registered nurse anesthetist (CRNA) or an anaesthesiologist’s assistant who is under the supervision of an anaesthesiologist who is immediately available if needed. Although those regulatory guidelines conflicted with guidelines published by some specialty societies, this policy initially shifted much of the sedation provision in the USA, and in many circumstances eliminated the delivery of deep sedation by registered and advanced practice nurses. A revision in 2011 sanctioned the institution to determine the qualifications of the sedation provider—acknowledging that individual hospitals can establish their own policies in accordance with recognized guidelines of specialty societies. This revision was important because it removed government restriction on sedation provision and re-aligned them with national specialty guidelines.

The economics of anaesthesia-delivered sedation in the USA is a topic of interest and concern. Between 2003 and 2009, anaesthesia services for gastrointestinal endoscopies increased by more than 50% for patients with commercial insurance. Anaesthesia services accounted for a two- and four-fold increase in Medicare and commercial payments, respectively (Fig. 1). A review in 2013 estimated that worldwide, if anaesthesia delivery for gastrointestinal endoscopy procedures was able to prevent a sedation-related death, it would be at a cost of US $5 million per life-year saved. A computer assisted personalized sedation (CAPS) device (Sedasys. Ethicon Endo-Surgery, Cincinnati, OH, USA) was approved in January 2014 for non-anaesthesia delivery of propofol to healthy (ASA I and II) adults for routine endoscopy and oesophagogastroduodenoscopy procedures. With anaesthesia-administered sedation for routine endoscopy projected for 50% of the patients in 2015, this technology could have significant financial implications by reducing the current US $2 billion annual anaesthesia expenditures for such services. To date, there has not been an assessment of preventable morbidity, improved safety or difference in health care costs between anaesthesia and non-anaesthesia delivery of paediatric procedural sedation. Particularly in the low-risk (ASA I or II) patient, large multi-centre studies are needed to demonstrate whether there are differences in outcome with anaesthesia delivery.

In the majority of Europe, there is also no consensus on sedation practice between or within specialties or individual countries: The Netherlands, Scotland and the UK have each recently published paediatric sedation guidelines. In the Netherlands, the Dutch Institute for Healthcare Improvement commissioned the 2011 Pediatric Guidelines for Procedural Sedation, Analgesia, or both at Locations Outside the Operating Theatre from the Netherlands Society of Anaesthesiologists and the Dutch Society of Pediatrics. In the UK, the National Institute for Health and Clinical Excellence developed in 2010

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**Fig 1** Volume of potentially discretionary anaesthesia service use and associated payments among commercially insured patients during 2003–2009. ©2012 American Medical Association. All rights reserved.
the Guidelines for Sedation for Diagnostic and Therapeutic Procedures in Children and Young People, and in 2013 the Academy of Royal Medical Colleges published Safe Sedation Practice for Healthcare Procedures with paediatric application.121 122 These guidelines are unique in that they recognized inhalation anesthetics (Sevoflurane) as appropriate for moderate and deep sedation by non-anaesthesiologists.

To date, there are no sedation guidelines published specifically from Asian countries. Most of the Asian countries follow ASA, American College of Emergency Physicians, American Academy of Pediatrics, and Joint Commission guidelines. Some countries are currently embarking on creating their own sedation guidelines (Japan, China). In the South Pacific, the Australasian College for Emergency Medicine, and Australian and New Zealand College of Anaesthetists have published a ‘Statement on Clinical Principles for Procedural Sedation’.123 The South African Society of Anaesthesiologists published Paediatric Procedural Sedation and Analgesia Guidelines in 2011.5

Training, credentialing and maintenance of sedation skills

In the USA, the Joint Commission in 2007 made specific recommendations for training, specifying that providers be able to manage patients even from unintentionally achieved depths of sedation. Those delivering deep sedation, in particular, should be qualified to rescue and manage the cardiovascular, respiratory and airway complications that could accompany a general anaesthetic.124 Some societies have been proactive in their efforts to address the training needs of their members by publishing consensus statements and guidelines. This year gastroenterologists, in the USA, published a multisociety Sedation Curriculum for Gastrointestinal Endoscopy. This was a joint collaborative effort among four national gastroenterology societies to establish and maintain sedation proficiency.125 The American College of Emergency Physicians, ASA, American Dental Association, American Academy of Pediatrics, and American Academy of Pediatric Dentistry have also within the past few years published their own guidelines to address sedation training, delivery and credentialing of their members.6 90 91 92 99 101 104 126 127

Propofol-fuelled controversy

Propofol continues to fuel worldwide controversy, with conflicting guidelines and statements being published, and sometimes retracted. In the USA, the past 5 yr have witnessed the introduction of guidelines for the delivery, skill-set, credentialing, and monitoring of propofol administration by the non-anaesthesiologists of the Societies of Gastrointestinal Endoscopy and Emergency Medicine.7 14 106 108 110 112 126 The ASA accepts non-anaesthesiologists for propofol delivery only when an anaesthesiologist is unavailable. In 2009, the ‘Statement on Safe Use of Propofol’ advised that involvement of an anaesthesiologist is optimal for patient care but, when not available, the non-anaesthesia provider must be qualified to rescue from ‘…a state of general anesthesia’.94

This propofol controversy extends to Europe. In 2010, the European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology reached a consensus when they published the Guideline for Propofol Administration by Non-Anaesthesiologists.15 These guidelines were controversial and provoked an outrage amongst some anaesthesia societies throughout Europe. Eventually the European Society of Anaesthesiologists retracted its support for these propofol guidelines after the publication of a Consensus statement from 21 European National Societies of Anaesthesia that opposed this Guideline.16 17 Intended for adults, the aforementioned guidelines do not address children. In general, the majority of propofol delivery for procedural sedation in Europe is by anaesthesiologists, although it remains a topic of ongoing debate.17 128 129 In the Pacific rim area, the Australian and New Zealand College of Anaesthetists endorses propofol administration by non-anaesthesiologist medical or dental practitioners in their Guidelines on Sedation and/or Analgesia for Diagnostic and Interventional Medical, Dental or Surgical Procedures.130

Outcome studies of the safety of sedation

Currently, there is no substantial data to restrict sedation delivery to one specialty. Large outcome studies (usually retrospective) and meta-analyses, present outcomes of non-anaesthesia providers. A large, multi-centre study of 130 000 sedations provided by paediatrician and non-paediatrician providers, presented a low rate of adverse events.131 Other large multi-centre studies have demonstrated similar outcomes between delivery by anaesthesiologists, intensive care medicine physicians, emergency medicine physicians, and paediatricians.132

Some specialties have independently published their own outcomes. For example, the emergency medicine literature presents a 3.9% overall incidence of airway and respiratory adverse events with ketamine. A meta-analysis of 8282 paediatric ketamine sedations, pooled from 32 studies, demonstrated that high i.v. doses, age <2 yr or >13 yr, and co-administration of anticholinergics or benzodiazepines, independently predicted an increased risk of adverse events.133 Sedation delivery by dentists has become an area of scrutiny. Widely publicized office-deaths have identified significant risk to sedation in paediatric dental offices.134 135 It is estimated that there may be up to 250 000 paediatric dental sedations annually in the USA.136 Recently, two leading dental professional liability insurers in the USA reported that half of the events between 2003 and 2007 resulted in death or permanent brain damage in children <3 yr of age.137

The USA continues to remain the country with the greatest volume of non-anaesthetist delivered propofol in the world. As experience mounts, more outcomes are published from different specialties: oxygen desaturation, airway obstruction and apnoea are the more common serious adverse events, occurring with an overall 2.3% incidence when delivered by emergency medicine physicians.2 138 Similar outcomes have
been presented with more than 7000 propofol encounters by intensive care physicians (0.37% brief positive pressure ventilation, 0.03% intubation).\textsuperscript{139} Paediatric hospitalists report similar adverse event rates with 1649 propofol encounters (2 aspirations, 1 elective intubation in order to complete the procedure).\textsuperscript{140–141} Anaesthesiologists in Italy performed 17 999 sedations for paediatric gastrointestinal endoscopies, the majority administered as target controlled propofol infusions [targeted controlled infusion (TCI) propofol]. The 2.6% rate of adverse events was similar to those of non-analgesiologists.\textsuperscript{142} Data from 2527 patients in the Nordic countries who received nurse administered propofol showed a similarly low rate of significant adverse events (0.9% positive pressure ventilation, no tracheal intubations or cardiac arrest).\textsuperscript{143} To date, the data supports paediatric sedation with propofol by trained providers with well-defined protocols.

### Drug shortages affect delivery of sedation

Limited supplies and discontinuation of the manufacture of some sedatives are challenging the sedation provider to find alternative methods of sedation (drugs, routes, and methods).\textsuperscript{144} In 2012 and 2013, two of the major manufacturers of chloral hydrate in the USA notified the FDA that they would be discontinuing its manufacture, a business and not safety decision.\textsuperscript{145} In 2009, the USA experienced a shortage of propofol that prompted the FDA to temporarily allow the European formulation Fresenius Propoven 1% to be imported from the European Union despite its lack of formal FDA labeling and differences in formulation.\textsuperscript{146} Shortages of ketamine and etomidate, during periods when they were listed on the FDA Drug Shortage list, additionally challenged the provision of sedation in the USA.\textsuperscript{147–148} These shortages highlight the need to develop new sedatives, consider different routes and methods of administration, prioritize the need to pursue paediatric labelling for eligible sedatives, and be creative to determine solutions.

### Role of simulation

Future initiatives and developments in sedation should involve incorporation of simulation into training, credentialing and maintenance of sedation skills. The value of simulation dates back to World War I, when pilots, crew and air traffic controllers were trained with simulation.\textsuperscript{149} Simulation offers a hands-on experience, re-creating both relatively common (airway obstruction, laryngospasm, and bronchospasm), and rare (cardiovascular collapse, aspiration, and anaphylaxis) situations. Simulation can range from simple re-creation of clinical scenarios using human volunteers to expensive simulation centres with high-fidelity mannequins.

Simulation training can be tailored to the specialist, patient population, procedure type, setting (hospital vs outpatient, ambulatory setting), and type of sedation administered. Simulation can not only develop the sedation provider’s management skills, but also identify methods to predict and prevent adverse events and develop teamwork. The ability to utilize, organize and direct a team is important in crisis management.\textsuperscript{150} Recent literature from different specialties demonstrates that simulation is important for training and can have long-lasting effects on the improvement of sedation-related skills.\textsuperscript{151–157}

Future efforts should be made to identify the best means to incorporate simulation into the field of sedation, so that it is available, affordable and beneficial to all providers. Although there is widespread agreement that simulation is important, to-date there are no national or international recommendations or programmes to guide the application of simulation for sedation. A recent European initiative focuses on the role of training and competency in sedation: The European Society of Anaesthesiologists has recently presented an initiative to provide an updated evidence-based guideline on how to provide sedation in a safe way to children. This workgroup will use the Grading of Recommendations Assessment, Development and Evaluation approach to evaluate the literature to develop evidence-based recommendations.\textsuperscript{152} The group will focus mainly on competencies that the sedation provider needs in order to make the procedure safe. If evidence is lacking, the consensus between experts will address the problem. It is hopeful that this initiative will guide and prioritize the skills necessary for safe sedation.

### Do sedatives affect neurodevelopment?

There remain unanswered, important questions regarding the safety of sedation. A topic of ongoing interest has been the potential effect of anesthetic agents on neonatal and infant neurodevelopment.\textsuperscript{159–160} Multi-centre studies are currently ongoing to determine whether there are long-term effects of certain anaesthetics. Studies in rodents and primates suggest that inhalation anesthetics and ketamine affect neuroapoptosis during sensitive times of brain development,\textsuperscript{161–164} but that dexmedetomidine may be neuroprotective.\textsuperscript{165–166} Currently the large, multi-centre studies designed to assess the effect of anesthetics on neurocognitive development, do not include commonly used sedatives such as dexmedetomidine, propofol, benzodiazepines, and ketamine.\textsuperscript{167–168} The sedation community must unite to design studies intended to evaluate the effect of some of the more commonly used sedatives on neuroapoptosis and cognitive development in infants and children. A relationship between neurocognitive outcome and sedative agents could guide not only the future delivery of sedation but also the choice on whether and when to perform non-urgent procedures on infants ‘at risk’.

### Sedatives in development: new drugs, routes, delivery systems

Over the past decade, there has only been one new sedative, dexmedetomidine, introduced worldwide, and no sedative with paediatric labelling. There is no current sedative that is ideal with respect to pharmacokinetics, pharmacodynamics, predictability, safety, patient satisfaction, and sedation profile. New sedatives, routes, and methods of delivery need to be explored. There are some sedatives in development that could offer benefits.
Most sedatives in development are pro-drugs of those currently available. For example, HX0969W is a water-soluble pro-drug of propofol that releases propofol and gamma hydroxybutyrate. Studies in rodents suggest that it has a longer onset time and shorter duration of action than fospropofol.66 169 HX0969W modified by adding a glycine or alanine to the structure, identified as HX0969-Gly-F3 and HX0969-Ala-HCl, has been tested in vitro. Initial studies suggest that without the phosphate ester, these prodrugs eliminate the paresthesias, pruritus and perineal burning that has been associated with propofol and fospropofol while producing quicker onset of action and an improved safety profile.170

Another agent in development is remimazolam. This is an ultra-short acting benzodiazepine that is currently undergoing trials as a procedural sedation agent. It appears from initial studies to have a more rapid onset and a shorter recovery time than midazolam.171–173

Derivatives of etomidate are in development, intended to modify the pyrrole ring responsible for adrenocortical suppression. Methoxycarbonylmoc-etomidate is reported to offer a stable haemodynamic profile, fast onset and rapid metabolism.174 Carboetomidate contains a five-membered pyrrole ring instead of an imidazole. The loss of the free imidazole nitrogen eliminates coordination interactions with heme iron, thereby reducing adrenal suppression.175 In vitro studies suggest that modifications to etomidate’s chiral centre reduce the adrenocortical suppression.176 177

Emulsified forms of inhalation anesthetics, available for i.v. delivery, might introduce a new approach to sedation. Emulsified isoflurane is being developed in China and currently has begun Phase I trials. Escalating doses have been shown to produce fast onset, increasing depths of sedation and fast recovery.178 179

New routes and methods of delivery, using either new or existing sedatives, might also offer benefits. For example, sublingual sufentanil with a profile similar to parenteral administration, is being developed.180 Intranasal and intramuscular dexmedetomidine, non-approved routes of delivery, have been described with success for the off-label paediatric patient population.66 181–184 New methods of sedation delivery using TCIs, a common method in Europe and Asia of delivering anaesthesia, could offer benefits. If the pharmacokinetics of a sedative are defined, as is already the case with propofol and remifentanil, it can be delivered to achieve a targeted blood concentration (brain) using validated pharmacokinetic models. Incorporating the bispectral index into the computer algorithm might offer an improved means of achieving and maintaining a targeted sedation depth.185 Currently TCI delivery pumps are approved and in use outside of the USA. Further development of paediatric models for TCI delivery, could provide a means of delivering sedation in a more precise, efficient and safe method. Future studies should focus on the benefits of TCI over manual titration of sedation.

Currently, a computer-assisted personalized sedation device marketed as SEDASYS, has been developed and recently FDA approved (May 2013) for the moderate sedation of healthy adults during gastrointestinal endoscopy.173 186 SEDASYS integrates patient data (electrocardiogram, non-invasive blood pressure, capnography, respiratory rate, pulse oximetry, and patient responsiveness to verbal stimuli) into computerized programs in order to guide drug delivery. In the USA, it has been released on a limited basis since early 2014.187 Future studies are needed to determine whether this system could be applied or modified to paediatric use.

A distant look into the future, reminiscent perhaps of Jules Verne in the 1800s when he fantasized of submarines and aircraft in 20 000 Leagues under the Sea and From the Earth to the Moon, respectively, might reveal applying pharmacogenetics to sedation practice. Pharmacogenetics has already been shown to have a role in the effect of propofol, dexmedetomidine, opioids, non-opioid analgesics, benzodiazepines, analgesic, sedative, and local anesthetic medications.188–195 In the future, knowledge of pharmacogenetics might enable tailored sedation to the genetic ‘fingerprint’ of a particular person.

Challenges to the advancement of paediatric sedation

Children represent an at-risk population by virtue of the fact that many of the sedatives they receive are used off-label, having not undergone the necessary rigorous studies to meet approval for paediatric use. For example, ketamine, etomidate, chloral hydrate, pentobarbital, and dexmedetomidine are being administered off-label. The USA first addressed this disparity between adult and paediatric prescription with the Best Pharmaceuticals for Children Act of 2002. This Act incentivized drug companies to conduct FDA-requested paediatric studies by rewarding an additional 6 months of marketing exclusivity. The Pediatric Research Equity Act of 2003 defines conditions for which the FDA may require drug companies to conduct studies of their products.196 Despite these initiatives in the United States, there is a paucity of paediatric labelled sedatives. Midazolam received paediatric labelling in 1998 and propofol was the last sedative to obtain paediatric approval in 1999.

The design of paediatric sedation studies for those pursuing paediatric labelling has become a topic of increasing interest by the FDA. In 2012, the FDA created a new Sedation Consor- tium on Endpoints and Procedures for Treatment, Education, and Research (SCEPTER) to develop evidence-based consensus recommendations for clinical trial designs, including efficacy and safety endpoints, for adult and paediatric procedural and intensive care unit sedation products. The SCEPTER group represents a multidisciplinary Steering Committee of sedation experts (clinical and researchers) from diverse medical specialties within the USA, Europe and Asia. The Committee includes anaesthesiologists, gastroenterologists, intensivists, emergency room physicians, and oral surgeons.197 The SCEPTER group has met twice and is actively working to advise the FDA on future sedation trial designs. It is hopeful that this initiative will not only encourage sedation trials but also, more importantly, ensure that the studies are optimal in design and outcome assessment.

Currently, there is lack of conformity and agreement between specialists on sedation guidelines, recommendations
### Step 1: Was there one or more adverse events associated with this sedation encounter?
- No, this form is now complete.
- Yes, fill out remainder of form below.

### Step 2: Please DESCRIBE the adverse event(s). Check all that apply.

<table>
<thead>
<tr>
<th>Minimal risk descriptors</th>
<th>Minor risk descriptors</th>
<th>Moderate risk descriptors</th>
<th>Sentinel risk descriptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting / Retching</td>
<td>Oxygen desaturation (75–90%)</td>
<td>Bag valve mask-assisted ventilation</td>
<td>Oxynge desaturation, severe (&lt;75% at any time) or prolonged (&lt;90% for &gt;60 s)</td>
</tr>
<tr>
<td>Subclinical respiratory depression</td>
<td>Apnoea, not prolonged</td>
<td>Laryngeal mask</td>
<td>Apnoea, prolonged (&gt;60 s)</td>
</tr>
<tr>
<td>Muscle rigidity, myoclonus, hypokinesia</td>
<td>Airway obstruction</td>
<td>Oral/nasal airway</td>
<td>Cardiovascular collapse/shock</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>Failed sedation</td>
<td>CPAP</td>
<td>Cardiac arrest/absent pulse</td>
</tr>
<tr>
<td>Paradoxical response</td>
<td>Allergic reaction without anaaphylaxis</td>
<td>or the administration of: Reversal agents</td>
<td>Other, specify below</td>
</tr>
<tr>
<td>Recovery agitation</td>
<td>Bradycardia</td>
<td>Rapid i.v. fluids</td>
<td></td>
</tr>
<tr>
<td>Prolonged recovery</td>
<td>Tachycardia</td>
<td>Anticonvulsant i.v.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seizure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Step 3: Please note the INTERVENTIONS performed to treat the adverse event(s). Check all that apply.

<table>
<thead>
<tr>
<th>Minimal risk</th>
<th>Minor risk</th>
<th>Moderate risk</th>
<th>Sentinel intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>No intervention performed</td>
<td>Airway repositioning</td>
<td>Bag valve mask-assisted ventilation</td>
<td>Chest compressions</td>
</tr>
<tr>
<td>Administration of: Additional sedative(s)</td>
<td>Tactile stimulation or the administration of: Supplemental oxygen, new or increased</td>
<td>Laryngeal mask</td>
<td>Tracheal intubation or the administration of:</td>
</tr>
<tr>
<td>Antiemetic</td>
<td>Antialoque</td>
<td>Oral/nasal airway</td>
<td>Neuromuscular block</td>
</tr>
<tr>
<td>Antihistamine</td>
<td></td>
<td>CPAP</td>
<td>Pressor / epinephrine</td>
</tr>
<tr>
<td>Antiseudomain</td>
<td></td>
<td>or the administration of: Reversal agents</td>
<td>Atropine to treat bradycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rapid i.v. fluids</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anticonvulsant i.v.</td>
<td></td>
</tr>
</tbody>
</table>

### Step 4: Please note the OUTCOME of the adverse event(s). Check all that apply.

<table>
<thead>
<tr>
<th>Minimal risk outcome</th>
<th>Minor risk outcome</th>
<th>Moderate risk outcome</th>
<th>Sentinel outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adverse outcome</td>
<td>Unplanned hospitalisation or escalation of care</td>
<td>Death</td>
<td>Permanent neurological deficit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pulmonary aspiration syndrome</td>
</tr>
</tbody>
</table>

### Step 5: Assign a SEVERITY rating to the adverse event(s) associated with this sedation encounter.
- If there are any options checked in the Sentinel column above, then this is a Sentinel adverse event.
- If the most serious option(s) checked above are Moderate risk, then this is a Moderate risk adverse event.
- If the most serious option(s) checked above are Minor risk, then this is a Minor risk adverse event.
- If the most serious option(s) checked above are Minimal risk, then this is a Minimal risk adverse event.

Additional details (including ‘other’ entries):

Footnotes:

a. “Subclinical respiratory depression” is defined as capnographic abnormalities suggesting respiratory depression that do not manifest clinically.

b. “Paradoxical response” is defined as unanticipated restlessness or agitation in response to sedatives.

c. “Recovery agitation” is defined as abnormal patient affect or behaviors during the recovery phase that can include crying, agitation, delirium, dysphoria, hallucinations, or nightmares.

d. “Prolonged recovery” is defined as failure to return to baseline clinical status within 2 hours.

e. “Failed sedation” is defined as inability to attain suitable conditions to humanely perform the procedure.

f. Alteration in vitals signs (bradycardia, tachycardia, hypotension, hypertension) is defined as a change of >25% from baseline.

g. “Cardiovascular collapse/shock” is defined as clinical evidence of inadequate perfusion.

h. Examples of “escalation of care” include transfer from ward to intensive care, and prolonged hospitalisation.

i. “Pulmonary aspiration syndrome” is defined as known or suspected inhalation of foreign material such as gastric contents into the respiratory tract associated with new or worsening respiratory signs.

j. “Sentinel” adverse events are those critical enough to represent real or serious imminent risk of serious and major patient injury. Once recognized, they warrant immediate and aggressive rescue interventions. Once clinically concluded, they warrant immediate reporting within sedation care systems, and the highest level of peer scrutiny for continuous quality improvement.

k. “Moderate” adverse events are those that, while not sentinel, are serious enough to quickly endanger the patient if not promptly managed. Once clinically concluded, they warrant timely reporting within sedation care systems, and periodic peer scrutiny for continuous quality improvement.

l. “Minor” adverse events are those encountered periodically in most sedation settings, and that pose little threat given appropriate sedationist skills and monitoring.

m. “Minimal” adverse events are those that alone present no danger of permanent harm to the patient.

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Fig 2: Adverse sedation event-reporting tool[^199], by permission of Oxford University Press.

[^199]: This is a reference to a specific tool or method used for reporting adverse events during pediatric procedural sedation. The tool is likely a structured form or checklist designed to help healthcare providers systematically record and categorize adverse events associated with sedation procedures. The example given includes various categories of adverse events, their descriptions, and corresponding interventions and outcomes, along with a severity rating system to help prioritize and manage reported incidents effectively. The tool emphasizes the importance of comprehensive documentation and continuous quality improvement in sedation practice to ensure patient safety and optimize clinical care.
and practice. Of the 53 countries of Europe, only a handful have published sedation guidelines, most of which were only intended for specific specialties. This lack of conformity is partially a reflection of inadequate large, multicentre, multi-specialist delivered sedation studies to provide outcomes that support the design of evidence-based guidelines. A first step to achieve these goals would be to establish a clear definition of specific sedation-related outcomes that could be applied to future studies. Currently, sedation studies are not uniform in their definition of outcomes. Terms such as hypoxia, apnoea, airway obstruction, oxygen desaturation, bradycardia, tachycardia, hypo/hypertension and failed sedation are outcomes with arbitrary, investigator-specified, definitions. The lack of universally accepted and utilized clear definitions for significant outcomes on hypoxia, hypotension and unplanned airway intervention, hampers the ability to objectively evaluate and compare outcome and sedation practice.198

The International Sedation Task Force (www.InternationalSedationTaskForce.com) is comprised of sedation experts representing both adult and paediatric specialties from around the world. This Task Force reached a consensus on the definitions of sedation-related adverse events (Fig. 2) along with possible interventions that can be utilized to relieve them. Published in the British Journal of Anaesthesia,199 this consensus was translated to an open access, web-based Adverse Event Sedation Reporting Tool that is free of Protected Health Information, in compliance with the Health Information Portability and Accountability Act (HIPAA). This website, www.AESedationReporting.com, is accessible to all sedation providers—a means of collecting, organizing and accessing an individual’s data along with the collective data of all those who have contributed.199

Another initiative that could improve collection of objective data would be a reevaluation of the Sedation Continuum.96 An important limitation of the Sedation Continuum, albeit an accepted method to define the depth of sedation, is that it relies on subjective data. It requires that the patient be stimulated with verbal, tactile or painful stimuli in order to assess sedation depth. In many cases, stimulating a sedated child is impractical (child in a MRI scanner) and could awaken the child, thereafter compromising the ability to successfully complete the study or necessitating administration of additional sedatives for procedure completion. Using the Sedation Continuum as a measure of sedation, necessitating continuous re-evaluation of sedation depth, is not always a practical expectation. Why is depth of sedation so important, other than to determine a patient’s ability to tolerate the stimulation of the procedure (audio, tactile and pain)? The Sedation Continuum has never been validated as being predictive of the risk of adverse outcomes. That there is a causal relationship between depth of sedation and outcome is currently being questioned by those in the anaesthesia community, many of whom support the need for a large, randomized trial to determine whether sedation depth dictates risk.200

Green and Mason have advocated adoption of a new objective scale, Objective Risk Assessment Tool for Sedation (ORATS), as a future means of assessing and predicting the risk of adverse events (Table 1). ORATS would use physiological data in conjunction with their newly proposed Comfort Assessment Tool for Sedation (CATS) in order to assess and stratify sedation risk.201 One such example is the current evaluation of the role of capnography to predict and reduce adverse events, with recent contributions to the literature.202–207 Although we believe that capnography will contribute to safer sedation care, to date there are no studies to support that capnography decreases the incidence of clinically relevant hypoxia and subsequent morbidity.

Physiological monitors that use novel technologies, such as non-invasive cardiac output monitors, bispectral index, transcutaneous carbon dioxide and near-infrared spectroscopy (NIRS) monitors can all be incorporated into such a tool—an objective means of determining whether a particular monitor can identify, predict or reduce risk.82 208–215 Collection of large objectively obtained data using ORATS and CATS from multi-specialists globally is one example of an important and necessary first step to determining the variables

<table>
<thead>
<tr>
<th>New levels (as yet unnamed)</th>
<th>Escalating risk of serious adverse event</th>
<th>Physiological monitoring parameters (singular or combination)*</th>
<th>Recommended provider skill set</th>
<th>Recommended resources†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤ 1:10 000</td>
<td>Consistent with normal awake pattern and frequency</td>
<td>Ability to observe and interpret the agreed-upon physiological monitoring parameters</td>
<td>Appropriate for risk level</td>
</tr>
<tr>
<td>2</td>
<td>1:1000</td>
<td>← Objective monitoring predicts this level of risk</td>
<td>Skills appropriate for maintaining sedation at this risk level and for rescuing from the subsequent level</td>
<td>Appropriate for risk level</td>
</tr>
<tr>
<td>3</td>
<td>1:100</td>
<td>← Objective monitoring predicts this level of risk</td>
<td>Skills appropriate for maintaining sedation at this risk level and for rescuing from the subsequent level</td>
<td>Appropriate for risk level</td>
</tr>
<tr>
<td>4</td>
<td>≥ 1:10</td>
<td>← Objective monitoring predicts this level of risk</td>
<td>Skills appropriate for maintaining a patient at this risk level</td>
<td>Appropriate for risk level</td>
</tr>
</tbody>
</table>

Table 1 Objective risk assessment tool for sedation.201, with permission from John Wiley and Sons. Preliminary sample schematic: the choice of four levels here is arbitrary and for illustration purposes only; the final tool would contain the minimum number of discrete levels with independent predictive value. Focused research would be required to validate the specific variables, parameters, and thresholds that predict the progressive levels of serious adverse event risk. Evaluation of capnography, for example, could include but not be limited to evaluation of waveform, frequency, pattern, numerical value on inspiration or expiration, or all. To be determined at each level by consensus panel and would include but not be limited to recommendations on adjuvant personnel, i.v. access, availability of rescue medications and airway equipment.
associated with sedation-related adverse events. A better appreciation of the risks and outcomes associated with various sedation techniques, patient populations, procedures and environments will aid in building a consensus for establishing evidence-based guidelines.

The history and evolution of sedation parallels that of the innovator Walt Disney who evolved his first animated cartoon of 1920 to the 1955 inauguration of the first theme park in the world, which to date has hosted more than 650 million guests. The field of sedation has similarly grown and evolved to become its own unique multi-disciplinary field—the delivery of which has and will continue to evolve and improve to meet and exceed the growing demands and needs of children. Each child that we care for should stimulate similar to that response described by Walt Disney when he visited his theme park: ‘... whenever I go on a ride, I’m always thinking of what’s wrong with the thing and how it can be improved...times and conditions change so rapidly that we must keep our aim constantly focused on the future.’ Similarly, the future of sedation depends on a collaborative effort of all sedation providers to objectively evaluate their sedation practice and put aside the politics and economics, in order to unite to determine optimal sedation practice within and between specialties.

Authors’ contributions

K.P.M. is the sole writer and researcher for this work.

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Declaration of interest

None declared.

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