Recommendations for the Use of Opioids in Children during the Perioperative Period

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Introduction:

The treatment of perioperative pain in children has been the subject of panel discussions and debate for many years. The role of opioid medications in the treatment of discomfort after surgery has been highlighted both as the critical component of adequate pain control and as the primary factor contributing to perioperative complications. Pediatric anesthesiologists are frequently called upon to address acute perioperative pain and therefore are often involved in ordering or directly administering opioid medications to children. In addition, pediatric anesthesiologists are a resource that can be utilized for oversight and planning of the more general use of these

medications within a healthcare facility and after discharge. Unfortunately, few evidence-based reports are available to guide the use of opioid medications in children. The evidence that exists is published in a wide variety of professional journals, newsletters, meeting proceedings, etc. With this in mind, the Society for Pediatric Anesthesia has supported the formulation of these recommendations with the intent of providing guidance for pediatric anesthesiologists that is (where possible) evidence-based, a synthesis of expert opinion, and based on clinical experience. These recommendations are intended to assist clinicians in making pain treatment decisions; they may be adopted, modified or rejected according to the clinical needs and constraints of the practitioner. Like any evidence-based, expert concensus recommendations, they are subject to revision as medical knowledge in this area evolves and evidence accumulates.

Definitions:

This document addresses the use of opioid medications (including assessment of pain and monitoring of patients on opioid therapy), adjunctive medications, and side effects related to opioid use. This discussion will be largely limited to pharmaceuticals available in North America, however, the principles of care apply to any medications in the opioid class. The "perioperative time frame" refers to administration immediately prior to, during, and following surgery, including the days following surgery that would be reasonably considered the recovery period for a given surgery that would be associated with discomfort.

Focus:

These recommendations are intended to address questions related to the use of opioid medications for children undergoing surgery or painful procedures. We have chosen to highlight the areas of appropriate monitoring and pain assessment since these aspects have high variability between care delivery systems and bear most directly on the safe use of these agents. Issues involving children with chronic pain or previous opioid use/exposure are also addressed since these patients are often the most difficult to manage in the perioperative time frame.

Purpose:

The recommendations in this document are intended to enable maximum patient benefit from opioid medications while maintaining a wide safety margin. Opioid medications provide analgesia and reduce distress for children undergoing painful procedures. Opioids have effectively allayed the immediate harm posed to infants and children who are in pain, severely stressed, and/or combative and thrashing about. Opioids can effectively mitigate future harms posed by untreated pain and anxiety, which can be emotionally traumatic and have life-long implications.[1,2] At the same time,

opioids are associated with a significant number of side effects, some simply annoying, others life-threatening. Efforts to speed anesthesia recovery and minimize common and potentially serious adverse effects have led some to advocate for avoiding opioids after brief but painful procedures such as tonsillectomy.[3] More worrisome effects including respiratory arrest and resultant cardiovascular collapse are well described in response to incorrect dosing or unusual patient characteristics. Finally, the current epidemic of opioid abuse has led many clinicians to seek methods to avoid exposure of at-risk individuals to opioid medications whenever possible.

These recommendations are focused on addressing the most pressing safety issues involved in the use of perioperative opioids for children with the intention to promote appropriate and safe practice, dispel unreasonable fear of their administration, and limit misuse. We hope this will result in the maximum benefit for patients who require potent pain relief in this setting.

Task Force Members and Consultants:

The SPA board approved the appointment of 9 primary authors to review the published evidence and reach consensus on issues related to the safe use of opioids in children. Those appointed come from a diverse array of institutions and sub-specialty backgrounds including pain medicine, clinical pharmacology, clinical trials, addiction medicine, general operating room anesthesia, and perioperative nursing. We also engaged 4 senior anesthesiologists with extensive histories of contribution to the specialty of pediatric anesthesiology with respect to pain management and opioid drug investigation to assist in reviewing/editing the recommendations.

Availability and Strength of Evidence:

The strength of evidence available for specific recommendations was based on a three-tiered classification system: Level A = based on prospective, randomized, blinded trials that meet the highest standards for investigation and reporting. Level B = based on prospective, observational data or appropriately conducted retrospective analysis with consideration of appropriate confounders and compensation for the influence of these factors. Level C = based on case reports, case series, or consensus of opinion involving experts who have a well-defined process for formulating conclusions.

For each recommendation, we have taken the level at which the preponderance of evidence was derived and clearly designated it as such. We sought clear consensus from our expert panel on the level of evidence for each recommendation and only present recommendations where there was consensus.

Age Related Opioid Effects:

The effectiveness of opioid analgesia and the side effects associated with their use vary with age. Multiple investigators have evaluated opioid pharmacokinetics and pharmacodynamics using (primarily) observational methodologies. Among these studies there is a poor correlation between measured blood opioid concentrations and patient analgesia. Many factors contribute to this variability. Most prominent among these factors is that pain perception is subjective (anxiety and constitutional pain sensitivity play a role) and the tools used to study pain in children vary widely. The ability to codify pain states differs greatly with age and developmental status, which further confounds pain assessment.

Pharmacokinetics/Pharmacodynamics of Morphine in Children:

Morphine is a commonly employed agent for pain control in newborns, infants, and children. There is consistent evidence that the greatest variation in pharmacokinetic parameters occurs in neonates and very young infants. Neonates have a larger volume of distribution and decreased protein binding which results in a greater free fraction of the opioid. Glomerular filtration rate (GFR) and hepatic enzyme development are relatively immature in neonates (0-28 days of life) resulting in a decreased clearance of morphine at about one-fifth to less than one-tenth of that in older children and adults.[4,5] There is considerable evidence from multiple observational trials that indicate that morphine clearance is increased via glucuronidation in older children when compared to neonates.[6] Notably neonates have consistently been shown to have at least a 50% lower glucuronidation rate and correspondingly lower clearance. In one study, following a single intravenous dose of morphine (0.1 mg/kg) to 20 neonates with a gestational age of 26-40 weeks, the free fraction of drug was 80% compared to 65% in adults. This finding combined with lower morphine clearance mandates longer dosing intervals in this age group.[7,8] In addition, the primary metabolite of morphine (morphine-6-glucoronide (M-G-6)) has a greater analgesic and respiratory depressant effect than morphine. These effects are amplified in the setting of decreased renal clearance that typifies neonatal pharmacokinetics.[9] Finally opioid dosing should take into consideration that the blood brain barrier is more permeable in neonates, leading to the potential for less fat soluble opioids to cause increased risk of respiratory depression. Using a non-linear dosing regimen, a relatively predictable serum level of morphine can be achieved in pediatric patients in spite of a broad range of clearance capabilities.[10] An evidence-based model has been validated using multiple large datasets involving pediatric patients who received morphine for pain control.[11] A dosing regimen based on this model has been prospectively validated.[12] In this regimen, doses for neonates under 10 days of life receive a 50-70% lower dose compared to commonly accepted standards recommendations. Efficacy has been shown to be maintained with this regimen while risk of overdosing is decreased. Consideration should be given to

specific patient pathology – such as increased intra-abdominal pressure, which may further delay clearance due to changes in hepatic blood flow.[13] Maturation of clearance and underlying metabolic pathways occurs relatively rapidly and reaches the levels of older children by approximately 6 months of age.[4,9,13] Children 2- 11 years of age actually have a higher clearance rate and larger volume of distribution than older children or adults.[14]

Recommendation: A validated, age-adjusted morphine dosing regimen should be used for all pediatric patients but particularly for neonates or where the dose and dosing interval will need to be altered significantly.

***Strength of Evidence*:** A.

Pharmacokinetics/Pharmacodynamics of opioids in general:

There is much less evidence concerning pharmacokinetics and pharmacodynamics of opioids other than morphine. Information on the clearance of fentanyl, sufentanil and alfentanil indicate that the clearance of fentanyl and sufentanil increases significantly from the neonatal to infant (greater than 28 days and less than one year of age) developmental period.[15,16] Additionally, there is evidence that premature and term neonates have considerably lower clearance of alfentanil when compared to infants and children.[17] On the other hand, remifentanil clearance is greatest in neonates and decreases with age while volume of distribution has an opposite trend yielding half-lives that appear similar across all age groups. [18]

Recommendation: Dosage of opioids other than morphine (discussed in previous section) should be decreased in neonates during the first 2-4 weeks of life (and for premature neonates until at least 42-44 weeks post conceptual age) - except for remifentanil, where the effective half-life in neonates is similar to that of older children and adults due to its increased clearance in that age group.

***Strength of Evidence*:** B.

Respiratory depression:

Evidence concerning the respiratory depressant effects of opioids is sparse. In one study, Lynn et. al. evaluated the respiratory depressant effects in 30 newborns-toddlers receiving morphine infusions after cardiac surgery. No age-related differences in respiratory effects were observed at similar morphine concentrations.[19] Similarly, in a small study of pediatric patients (11 days to 7 years of age) receiving morphine after major surgery, Okklola et. al. found no difference in the respiratory depressant effects of morphine between the youngest and oldest patients.[4] In a study of fentanyl related respiratory depression, Hertzka et. al. followed the respiratory depressant effect of

fentanyl as patients awoke from fentanyl/nitrous anesthesia. Elevation of $PaCO_2$ correlated with increasing plasma fentanyl concentrations but did not differ between groups of infants vs. children (1-5 years) vs. adults.[20] There was one case of respiratory depression without elevated fentanyl level in a 3-month-old infant. The authors concluded that there is no evidence of increased sensitivity to respiratory depression in children over 3 months of age when compared to older children or adults. On the other hand, a case review of pediatric patients with opioid-related respiratory depression found that age less than one year is an independent risk factor. Other similar reports lacked serum drug level data.[21]

Recommendation: Term infants (older than 3 months of age) do not appear to be at increased risk of respiratory depression due to opioids when compared to older children and adults *at the same blood level of opioid*. The dose of opioids (dose/kg) should be similar to older infants and children after 6 months of age (taking into account underlying health and previous exposure to opioids). When beginning opioid dosing in infants younger than 3 months of age, care should be delivered in a highly monitored environment (in many cases this would include a step down unit or ICU/NICU).

Strength of Evidence: B

The Use of Patient Controlled Analgesia (PCA)

Introduction - PCA vs. intramuscular (IM) opioid delivery:

PCA delivery of opioids has become the standard for analgesia after major surgery in children. This section will compare this delivery method vs. other opioid delivery modalities. There are many studies comparing PCA to IM opioids, including a meta-analysis[22] that revealed a higher level of patient satisfaction and lower pain scores for patients utilizing PCA. Few of these were randomized controlled trials that included pediatric patients.[23-25] The meta-analysis examined 15 randomized controlled trials including 787 adult patients finding greater patient satisfaction and an improvement in pain relief as reported by visual analog scale (VAS) scores and no difference in side effects. In the three pediatric studies, one compared PCA to IM morphine in 82 patients undergoing major orthopedic procedures, another compared these routes in 10 patients undergoing spinal fusion, and the third compared IM meperidine to PCA nalbuphine and IV ketorolac in 30 children. These three studies found improved pain control with PCA as measured by VAS despite similar consumption of opioid equivalents. None of these studies found a higher level of adverse events for PCA use as compared to IM opioids and a study by Berde et al. found a higher level of sedation in the IM morphine group.

***Recommendation*:** The use of PCA opioid delivery is preferable to IM opioid delivery for perioperative pain control in pediatric patients. (See discussion of PCA by proxy below)

***Strength of Evidence**:* A (Randomized, controlled, open-labeled trials)

PCA vs. Intermittent IV opioids:

There were no randomized controlled studies identified that compared PCA with intermittent opioid administration in the pediatric population. A number of cohort studies supported the use of PCA as efficacious and with acceptable rates of adverse events in a variety of postoperative settings (abdominal, laparoscopic, thoracic, orthopedic surgery) and with a variety of opioid choices (meperidine, fentanyl, morphine).[26-39] Higher quality data exists for adult populations. Meta-analysis of randomized controlled trials in the adult perioperative population performed for the purpose of updating the American Society of Anesthesiololgist's (ASA) guidelines found no analgesic benefit of PCA over nurse-administered IV opioids.[40] A Cochrane review of 49 studies and 3,412 patients comparing patient controlled opioid analgesia to non-patient controlled opioid analgesia for postoperative pain showed that patients who received PCA reported lower pain scores (9 to 10 points lower on a 100-point VAS) and greater satisfaction, used more morphine equivalents (7 mg more in the first 24 hours) and had no difference in adverse events except for a higher incidence of pruritus (15% vs 8%).[41] The authors concluded that this provided moderate to low quality evidence that PCA is an efficacious alternative to non-patient controlled analgesia in the adult post-surgical population. Finally, Faerber et al. used propensity matched cohorts from a multicenter administrative database to evaluate major adverse events in children who had received either PCA or intermittent IV opioids and found that PCA was associated with a lower risk of cardiopulmonary resuscitation (CPR) or the need for mechanical ventilation.[42]

***Recommendation*:** PCA is safe, efficacious, and correlated with higher patient satisfaction compared to nurse administered intermittent intravenous opioid analgesia.

Strength of Evidence: B

Opioid selection:

A randomized controlled trial of morphine versus meperidine in 50 orthopedic patients 8-16 years old showed no difference in side effects, but lower numerical rating scale pain scores in patients receiving morphine.[43] Ketobemidone was shown to be equally efficacious and safe as morphine when administered by PCA in a randomized controlled trial of 60 children in Denmark aged 6 to 16, but it is not currently available in the United States.[44] A randomized controlled study of 60 children post-tonsillectomy compared tramadol to morphine, with poorer pain control, similar sedation levels, and lower nausea scores in the tramadol group.[45] Comparison of morphine and hydromorphone in a randomized controlled trial of 96 patients showed no difference in pain control as reported by VAS, morphine equivalents administered (assuming 1:5

potency ratio), or side effects (hypoxia, pruritus, nausea, urinary retention).[46] A retrospective study of 514 pediatric patients at a single center revealed more frequent conversion from morphine to hydromorphone most often due to pruritus and poor pain control, while nausea was the most common reason to switch from hydromorphone to morphine.[47]

In the most recent national survey available, involving members of the Society for Pediatric Anesthesia (SPA) published in 2010 and representing 252 institutions around the United States, morphine was available for PCA use at 100% of institutions while 75% also had hydromorphone and fentanyl available. Meperidine for PCA use was only available at 17% of institutions.[48]

The literature is inconclusive in this area but no opioid has been shown to be more effective than others for use in PCA analgesia. There is also no evidence that a particular opioid has consistently fewer side effects than others in spite of a number of randomized controlled trials.[43-46]

***Recommendation*:** There is insufficient and conflicting evidence to recommend the use of a specific opioid over another for PCA post-operative pain control, however, due to the risk of accumulation of toxic metabolites (normeperidine) that may cause seizures meperidine is not recommended by the expert panel other than to treat postoperative shivering.

***Strength of Evidence*:** B

Use of continuous infusion simultaneous with PCA:

Randomized controlled trials that have compared continuous opioid infusion with PCA to PCA alone have suggested that the addition of continuous infusion may have many possible effects on the overall impact of PCA therapy. Comparative studies (6 to 12 year olds post-appendectomy,[49,50] 5 to 20 year olds post elective spinal fusion for scoliosis,[51] school-age children post-lower extremity orthopedic surgery,[52] and 6 to 15 year olds post-appendectomy[53]) have not shown an overall improvement in pain scores with the addition of a continuous infusion. There is evidence of an increase in overall opioid usage and an increased level of sedation with continuous infusions. The impact on sleep has been variable – including data on O_2 desaturation. Some data indicate an increase in sleep duration,[49,50] but there has also been documentation of an interruption of normal sleep patterns in a single-center retrospective audit of 126 children.[54]

In terms of the risk of adding continuous infusion to PCA, a meta-analysis of randomized controlled trials (including both adult and pediatric patients) indicated that pediatric patients have an overall lower risk of serious adverse advents associated with continuous infusion combined with PCA when compared to the adult population.[55] This

finding may be confounded by routine use of continuous respiratory monitoring in the pediatric population[48] and does not necessarily reflect a lower risk of events without such monitoring. In fact, a logical interpretation of the data on this topic would conclude that the increase in sedation level and total dose of opioid delivered when continuous infusion is added could lead to a higher incidence of adverse events when continuous opioid infusion is added to PCA.

There are few high quality data sets examining the issue of continuous infusion plus PCA in children. One meta-analysis examining randomized controlled studies comparing PCA bolus versus PCA bolus plus background infusion for postoperative analgesia in children showed no difference in pain scores at 12 and 24 hours, opioid consumption, or risk of adverse events, but the quality of evidence was deemed to be low or very low. [56]

Recommendation: There is conflicting and insufficient evidence to indicate a difference in overall analgesia, sleep patterns, or adverse events with the addition of continuous opioid infusion to PCA in children. Use of a basal infusion should be individualized based on consideration of the clinical situation, pain severity, and risk factors.

Strength of Evidence**:** B

PCA-by Proxy (PCA-P):

"PCA" activation by someone other than the patient is, by definition, an oxymoron. At the same time, many pediatric patients are either developmentally or physically unable to activate their PCA pump and require assistance from a caregiver. The small frequent opioid boluses given via the PCA device can provide appropriate analgesia while also offering an efficient, safe (minimizes dose calculation error) and user-friendly delivery method for the individual who is directly responsible for care (PCA by proxy, also referred to as PCA-P or nurse controlled analgesia (NCA)). A retrospective study of 302 randomly selected children out of a possible 833 having received a postoperative PCA were grouped by PCA or PCA-P use and analyzed for opioid consumption and adverse events. While similar numbers of adverse events occurred in both groups more rescue interventions were needed in the PCA-P group. The PCA-P group also tended to be younger and had more medical co-morbidities.[57] A prospective 1-year observational study of 212 patients showed that PCA-P was effective for pain control, but adverse events did occur, notably the use of naloxone in 9 patients, 4 of which were for PCA related respiratory depression.[58] A large retrospective review of 10,079 patients (including 510 neonates) with an average age of 4 years, who underwent PCA-P analgesia revealed 39 serious adverse events that required resuscitation and naloxone administration. Of these 13 were neonates less than 3 months old and 4 were ex-premature neonates; no deaths occurred.[59] A dose-finding study of 30 infants and toddlers (6 months to 2 years of age) using parent controlled analgesia (PCA-Parent)

with fentanyl after cleft palate repair had no instances of over-sedation or apnea and only 3 patients with vomiting.[60] Still another study of 107 preschoolers and infants utilizing PCA-P (nurse and parent) analgesia showed 1.9% of those patients had a serious adverse event requiring naloxone administration.[61] PCA-P has also been investigated in the NICU in a single retrospective study of 20 infants compared to 13 who had fentanyl infusions. Infants with PCA-P had excellent pain control with pain scores less than 1 on a 10-point scale. The infants receiving PCA-P had a significantly lower opioid consumption than those on continuous infusion (84 % less morphine equivalents), but there was no difference in occurrence of adverse events or in subsequent methadone use.[62]

Use of *authorized* PCA-P (parent or proxy) has been reported to be a safe and effective method of postoperative analgesia delivery for patients who are unable to use PCA themselves due to age, mental status, developmental delay, or disability.[51,57-67] One randomized controlled trial of PCA vs. PCA with continuous infusion in children after spinal fusion showed (in a subgroup analysis) that nurses who performed PCA-P for patients unable use the PCA device themselves underestimated patient pain as compared to self-reported pain scores and administered less total opioid than patients self-administering medication.[51]

Unauthorized PCA-P appears to have resulted in rare sentinel events resulting in at least 5 fatalities and other injuries to at least 10 patients when family members or other caregivers (nurse, pharmacist) used the PCA device without authorization. It is unclear from the report what proportion of these events occurred in the pediatric population, or if any of the fatalities were children.[63]

***Recommendation*:** There is evidence that PCA-P may be an effective and safe method of providing perioperative analgesia when applied in an institutionally sanctioned program with appropriate training and monitoring.

***Strength of Evidence*:** B

PCA adjunctive Medications:

Ketorolac

A randomized controlled study of 68 children comparing ketorolac to placebo every 6 hours for 8 doses maximum showed a 47% reduction in fentanyl administered in the PACU by nurses as well as a 42% reduction in morphine administered by PCA after PACU discharge. The ketorolac group also had lower pain scores.[68] A previous study of 50 patients had found that a single dose of ketorolac intraoperatively was superior to placebo both in lower pain scores and in lower amount of morphine administered by PCA in the first 12 hours.[69] In both these studies side effects were largely similar and excess bleeding was not observed in the ketorolac groups. A study of 30 pediatric patients that compared ketorolac boluses at regular 6-hour interval to morphine PCA

showed similar pain scores for both groups overall, but changes in pain scores occurred more rapidly for children with a PCA as compared to conventional analgesia. The exact methodology was not well described in this report.[70] A case-control study comparing 29 children who received ketorolac plus morphine to children who received only morphine similarly found an opioid sparing effect of ketorolac without a difference in side effects.[71] A randomized controlled trial of 35 adolescents after spinal fusion showed lower postoperative pain scores, lower morphine consumption delivered by PCA, and no excess bleeding through postoperative day two.[72] In summary, short-term ketorolac administered in the postoperative setting decreases the amount of opioid administered by PCA and improves pain scores as compared to PCA alone, without evidence of excess postoperative bleeding, although these trials may not have been sufficiently powered to show small differences in the occurrence of bleeding events.

***Recommendation*:** The use of ketorolac should be strongly considered (in appropriate patients and in agreement with the surgical team) as an adjunct to PCA for pediatric perioperative pain control. Most evidence available for NSAID effect on PCA dosing involves ketorolac however there is good reason to assume another NSAID would have a similar PCA dose sparing effect.

***Strength of Evidence*:** A

Acetaminophen

A study of 80 children after appendectomy showed a significant morphine sparing effect with diclofenac, but a non-significant effect (17% less) with oral acetaminophen.[73] In contrast, a study of 63 children after ureteroneocystostomy, compared fentanyl and intravenous acetaminophen containing PCA to fentanyl-only PCA. Pain scores were similar between groups but a fentanyl sparing effect (53% reduction) was observed as well as lower incidences of vomiting and sedation in the fentanyl-acetaminophen group.[74] In another study of 36 patients after spinal fusion surgery, children receiving three postoperative doses of intravenous acetaminophen were compared to placebo. Those receiving acetaminophen showed a reduction in oxycodone consumption as administered by PCA and improved pain scores.[75]

***Recommendation*:** The use of acetaminophen, particularly intravenous, should be considered in appropriate patients as an adjunct to PCA for pediatric perioperative pain control.

***Strength of Evidence*:** A

Other adjunctive medications for pruritus are reviewed in the "Side Effects" section below.

Recommendations for Outpatient Post-operative Opioid Use in Children

Educational resources:

Despite all of the efforts to improve perioperative pain management in children, there is good evidence[76] that pain is poorly managed at home after hospital discharge. Data from multiple investigators indicate that children have been shown to report significant pain after many types of surgeries including tonsillectomy or adenotonsillectomy (T&A), dental extraction, and circumcision. Some studies suggest that parents may not give adequate pain medications to children for a number reasons-including: lack of information, inadequate understanding of perioperative opioid drug use, inadequate or inappropriate dosing, uncertainty of adverse effects including addiction, and child refusal.[77-79] Poor analgesic understanding can lead some parents to withhold opioids altogether to avoid risk or to administer opioids when children are excessively sedated.[80]

***Recommendation*:** Educational resources must be provided to inform parents of the appropriate indications for pain medications and strategies for the safe use of opioids, non-opioids and other measures to manage their child's post-operative pain. Parents should receive both verbal and written detailed discharge instructions regarding home pain management with instructions regarding safe storage and disposal of leftover medications.

***Strength of Evidence**:* B

Specific opioid therapy:

Unfortunately, there is very little pediatric literature upon which to formulate evidence-based recommendations for opioid dosing after surgery and discharge home. One exception is the strong evidence *against* the use of codeine in children undergoing tonsillectomy (or possibly all surgeries).[81,82,83] This conclusion is based on the fact that some children, depending upon ethnic origin, e.g. 1% of Northern European descent up to 29% of Ethiopians, will ultra-rapidly metabolize codeine to morphine resulting in high morphine levels even after appropriate codeine doses. There is also an FDA warning for nursing mothers to avoid codeine and to look for symptoms of possible overdose in infants if they breastfeed by mothers taking codeine. On the other hand, approximately 10% of individuals lack the ability to metabolize codeine to morphine and therefore realize little analgesic benefit from this drug. Similarly, while tramadol may be a useful opioid analgesic in many situations, it also uses the CYP2D6 pathways and may have variable effects depending on the allelic variation that is present in a given patient.[84,85] A further concern is the alteration of mu-receptors with chronic hypoxemia as

associated with obstructive sleep apnea (OSA) whereby children will experience effective analgesia with only one-third to one-half of a normal opioid dose thus placing children with OSA at particular risk even if normal doses of opioid are prescribed. [86,87]

***Recommendation*:** Codeine should be avoided in children and nursing mothers as a post-operative analgesic. This is particularly true if they have symptoms of obstructive sleep apnea or sleep disordered breathing.

***Strength of evidence**:* A

Recommendation: With the exception of codeine, there is insufficient evidence to recommend one specific opioid versus another in postoperative children.

Strength of Evidence: B

Dosing strategies:

There are only 2 randomized prospective studies evaluating the appropriate dosing of opioids in postoperative patients. In one study, Sutter et. al. compared "around the clock" (ATC) dosing to an "as needed" (PRN) strategy. In this case, patients who received around the clock acetaminophen with hydrocodone were compared to those who received the same medications "as needed" for complaints of pain. [88] There was improved pain control in the ATC cohort, but a slightly higher incidence of complications including a higher rate of daytime sedation in this group. A Cochrane review of ATC vs. "as needed" dosing,[89] found that more medication is administered in the ATC group, but the data were unclear as to whether or not pain management is improved. This review included three RCTs with a total of 246 children aged under 16 years undergoing tonsillectomy. There were no differences in pain relief or side effects between the two groups. The authors concluded that there was insufficient evidence to be certain which method is better for a child's pain relief after surgery. They noted that more high quality, large, studies are needed. Others have noted that ATC dosing of any opioid to children for whom CYP2D6 genotype is unknown may place children at risk for adverse events after discharge.[90]

***Recommendation*:** There is insufficient evidence to recommend PRN vs. scheduled dosing strategies for opioids after surgery in children. Expert consensus is to use a PRN strategy until further evidence is available.

Strength of evidence: C

Combinations of opioids and benzodiazepines:

A recent Food and Drug Administration (FDA) review determined that the use of opioid medications in combination with benzodiazepines in adults has increased and that this practice has resulted in serious side effects (http://www.fda.gov/downloads/Drugs/DrugSafety/UCM518672.pdf). Two studies are highlighted in this statement. The first found that the number of opioid analgesic prescriptions increased 8 percent and the annual number of benzodiazepine prescriptions increased by 31 percent.[91] The percent of patients receiving overlapping prescriptions for these two medications has increased by 41 percent. The second study found that between 2004 and 2011 the rate of opioid overdose deaths in which benzodiazepines were also implicated increased from 18 percent to 31 percent;[92] no similar pediatric data have been reported.

Recommendation: Opioid pain medications should be prescribed with benzodiazepines only in children for whom alternative treatment options are inadequate. Doses should be limited to the lowest effective level and parents should be warned about the potential for excessive sedation and respiratory depression.

Strength of evidence: C – extrapolated from adult studies

Addition of Non-opioid analgesics:

A number of investigators have found that the addition of non-opioid analgesia can benefit patients who are (or would otherwise be) receiving opioids. El Fattah found a decrease in postoperative pain with the use of a preemptive analgesic combination (rectal diclofenac, IV paracetamol and IV tramadol) versus children who received no preemptive medication.[93] In addition, a controlled study by Mitchell compared the combination of acetaminophen with ibuprofen to acetaminophen with codeine in adults. There were lower VAS scores on postoperative day two, higher satisfaction and a lower overall rate of adverse effects in patients who received the non-opioid combination.[94] Still other investigators have called into question the use of *any* opioids after tonsillectomy and adenoidectomy, particularly if these childrens have received optimal non-opioid therapy and have pre-operative evidence of oxygen desaturation during sleep.[95]

***Recommendation*:** Oral opioids should be used in the minimal effective doses and only after optimizing the use of acetaminophen and non-steroidal anti-inflammatory medications.

***Strength of evidence**:* B

Opioid Prescribing

There is increasing concern and national attention regarding the misuse of opioids in children and adolescents. Several federal agencies and physician organizations have weighed in on this topic [Centers for Disease Control (CDC), Substance Abuse and Mental Health Services Administration (SAMHSA), American Medical Association (AMA)]. These organizations highlight the growing incidence of opioid overdose in pediatric patients, particularly teenagers. The most common source of prescription opioids is drug supplies from leftover prescriptions (family, friends, neighbors, etc.). Recent studies have found that children are prescribed amounts of opioids that significantly exceed the total administered at home with large amounts remaining. Parents have generally not received instructions regarding safe disposal of leftover opioids.[96]

Recommendation: Only the amount absolutely required for the expected period of severe pain after surgery should be prescribed. In addition, patients should be educated concerning the appropriate disposal of opioids used for this purpose.

Strength of evidence**:** C – based on consensus of the expert panel.

Opioid treatment of the chronic pain patient scheduled for major surgery

Many pediatric patients present for surgery with a history of chronic pain, be it pain related to "central sensitization", cancer pain, chronic orthopedic condition or other medical issue. Some of these children will be opioid dependent or tolerant to the effects of opioid analgesics given their treatment with these medications on a long-term basis. Others will come to the OR with opiate dependence based on misuse of prescribed opioids or recreational use of opioids. Still other patients are on opioid maintenance programs, methadone or buprenorphine, and (therefore) also require special consideration. There is little evidence to guide the treatment of these patients, but experience and reason demands appreciation of the unique challenges they bring to managing their perioperative pain.

In treating these patients it is critical to differentiate certain terms that are associated with chronic opioid use. *Physical dependence* describes the alterations in physiologic response that result from opioid binding and receptor mediated activity. In this subgroup, sudden discontinuation of opioids leads to opioid withdrawal or abstinence syndrome. On the other hand, *opioid tolerance* refers to the pharmacologic adaptation that occurs after chronic exposure to opioids where there is a shift in the dose-response curve and patients require increasing amounts of drug to maintain the same pharmacologic effects. Finally, *drug addiction* refers to a complex phenomenon where the use of a particular drug becomes the central point of focus for the user's life, i.e. deriving psychological reward other than analgesia, even in the face of obvious physical

or psychological harm. Patients who exhibit addiction are usually physically dependent on a particular opioid. Dependence and addiction may exist in conjunction with each other or as independent entities and must be identified and appreciated in order to appropriately (and safely) treat pain in this challenging population. [97]

Perioperative Care of Patients with Chronic Pain Disorders who are Taking Opioids:

Recommendations for pediatric patients presenting for surgery who are on opioids for chronic pain syndromes or who have chronic pain associated with central sensitization, (e.g., fibromyalgia), are entirely extrapolated from the adult literature. There are no studies examining perioperative care of pediatric patients currently using opioids, nor are there reports on the perioperative care of pediatric patients with fibromyalgia or other central sensitization syndromes. There is a single observational study showing that pediatric patients previously placed on opioid infusions in an intensive care unit do not have increased perioperative opioid requirements if they have previously been successfully weaned off the opioids. [98]

In the adult literature, recommendations for perioperative management of patients using chronic opioids are based on case reports, common sense, or consensus rather than randomized studies. Although not scientifically tested, these recommendations have been advocated in the setting of receptor down-regulation and appreciation of the physiological and psychological changes that accompany chronic pain and opioid treatment. In all cases, perioperative care is advised to begin with preoperative administration and continuation of the daily maintenance (or baseline) opioid dose. Additional doses of opioid should be titrated intra-operatively and postoperatively to provide effective postsurgical analgesia in addition to covering the baseline requirements.[97] Dosing guidelines are not available, but requirements to meet postsurgical analgesic requirements are affected by receptor down-regulation and may need to be increased by 30-100% in comparison to opioid naïve patients. Continuous opioid infusion or patient controlled analgesic (PCA) techniques are useful options in this subgroup. In the adult literature, a history of opioid abuse is not considered a contraindication to PCA use as long as opioid consumption is carefully assessed and adjunctive therapies such as baseline methadone dosing, non-opioid pain relievers (non-steroidals, gabapentin), and/or regional anesthesia techniques are employed. Alternative tolerance regarding medications such as dexmedetomidine and low dose ketamine have been used as an adjuvant therapy in highly tolerant patients with severe cancer pain. It is also worthwhile to consider the contributions of fear, anxiety, and depression to opioid consumption in these situations. These issues should be discussed transparently and treated with psychological and pharmacological interventions as indicated on a case by case basis.

Recommendation: For pediatric patients with chronic pain who are maintained on opioids, maintain established preoperative dosing during the perioperative period as a baseline. Acute post-surgical analgesia should be provided over and above the baseline opioids. Use of non-opioid analgesia is encouraged including regional analgesia techniques, alpha-2 agonists, ketamine, acetaminophen, nonsteroidal anti-inflammatory drugs, and neuropathic pain medications such as gabapentinoids or antidepressants.

Strength of Evidence: C – based on extrapolation of adult data and expert panel consensus.

Recommendation: If the chronic pain patient on chronic opioid therapy undergoes a procedure that is intended to remove the source of the patient's pain, they should be discharged home with a defined opioid weaning plan. Opioid weaning in this case should be managed by a physician with special training or expertise in pain medicine. Limited supplies of opioids should be prescribed and refilled at frequent intervals that include face-to-face follow up visits. If the patient's pain problem was independent of the surgery, the patient's baseline pain should continue to be managed by the physician who had been doing so preoperatively. Opioid analgesics for the perioperative pain, if needed, should be prescribed in limited quantities consistent with the degree of physiologic trespass.

Strength of Evidence (both): C – based on extrapolation of adult data and expert consensus.

Patients with Central Sensitization:

Perioperative management for pediatric patients with central sensitization is also largely based on consensus. There is evidence in adults with fibromyalgia that they are at risk for increased acute and chronic postoperative pain.[99,100] Opioid-related morbidity and mortality do not seem to be increased in these patients.

***Recommendation*:** For pain management of patients with central sensitization – strategies should be similar to those for patients on chronic opioids: use non-opioid analgesic techniques to the greatest extent possible. Opioids should be prescribed as needed. These patients benefit from the involvement of a pain physician for the purposes of assuring appropriate use and discontinuation of medications in a reasonable time frame.

Strength of Evidence C

Urine Testing

Urine drug testing has long been accepted as a part of the evaluation and treatment of chronic pain patients taking opioids and of those with opioid dependence/addiction.[101] While not well studied, the implications for anesthesiologists caring for opioid-managed patients and illicit users are fairly clear. One study of chronic pain patients found that 21% of those with behaviors suggestive of inappropriate medication use had positive drug screens for illicit drugs or non-prescribed medications. Of those *without* these behaviors 14% still tested positive for inappropriate drug use.[102] Few pediatric institutions have clear guidelines for the use of urine testing in these populations. In the only study available that specifically addresses this issue, a survey of Veterans Affairs Anesthesiology Chiefs determined that only 10% have a formal policy as to how to handle a positive perioperative drug screen for cocaine while over 80% felt that it was necessary to have such a policy.[103]

Recommendation: Urine drug screening should be considered for pediatric patients with a history of illicit drug use and those with chronic opioid intake with behaviors suggesting inappropriate use**.** Furthermore, hospitals should have formal policies for the management of a positive drug screen in the perioperative setting. Currently there is no (single) urine drug screen suitable for all clinical settings.

Strength of evidence: B

Addiction issues related/unrelated to perioperative opioid use

Prescribing Practice:

Opioid misuse and abuse have reached epidemic proportions in the United States among adolescents. Misuse of opioids falls in two categories: 1) Medical misuse of prescription opioids is defined as engaging in behaviors of opioid use not intended by the prescriber such as using too much to attain a euphoric state rather than pain control or using a given prescription for a condition it was not intended for. 2) Non-medical use of prescription opioids (NMUPO) refers to the non-prescribed use of prescription opioids. A national database examining adolescent drug abuse found that in 2014 [104] 6.1 % of 12th graders intentionally used an opioid other than heroin without a doctor's prescription at least once over the past year and over the course of their lifetime 9.5% of 12th graders have intentionally misused these opioids. Others have found that 20% of adolescents who had legitimately been prescribed an opioid in the past year reported later misuse.[105] Specifically, 2.2% misused extended release oxycodone, 1.9% misused hydrocodone-acetaminophen 1.6 % misused oxycodone-acetominophen, and 2.9 % abused hydrocodone. In this same survey 42.2 % of 12th graders and 18.8% of 8th graders believed that it was either "fairly easy" or "very easy" to obtain these opioids if they wanted, and most obtained the opioid from a friend or family member.[106] Data

from the Substance Abuse and Mental Health Services Administration (SAMHSA)[107] in 2011 note that, on an average day in the United States, 26 adolescents are admitted to emergency departments due to NMUPO and 2,151 adolescents use NMUPO for the first time.

There is equivocal literature to evaluate perioperative use of opioids in adults with iatrogenic dependence or addiction[108] and insufficient literature in adolescents. However, there are identified risk factors and physician prescribing behaviors that may be associated or contribute to NMUPO. In the 2013 National Survey on Drug Use and Health[109] it was noted that over 90% of misused opioids were from legitimate prescriptions which were either obtained directly from friends or relatives or from a prescriber. The primary risk factors contributing to adolescent NMUPOs are overprescribing (both in total amount and for non-legitimate cause), not disposing of opioids in a timely fashion [110] and giving adolescents unsupervised access to opioids in the home.[111]

Recommendation: (As noted in the "Outpatient" section above) Opioid prescriptions should be written only for the amount that is reasonably expected to be used in the immediate post-operative period. This is particularly important for patients/families at risk for misuse. These medications *should be secured in the home,* not readily accessible. Parents and patients should be informed on how to dispose of medications properly and they should understand the risks of saving these medications.

Strength of Evidence*:* B

Prediction of risk of misuse/abuse:

Strong evidence exists for utilizing assessment tools to predict NMUPO risk for patients prescribed opioids.[112,113] The CRAFFT tool, a mnemonic acronym for the six screening questions, is a validated tool that has acceptable reliability ($\alpha = .79$) and is highly correlated ($r = 0.84$) with the Personal Involvement with Chemicals Scale (PICS). A score of 2 or higher on the CRAFFT had sensitivity and specificity of 0.80 and 0.86, respectively, for detecting any substance abuse or dependence. Thus, regular utilization of the CRAFFT can identify pediatric patients (teenagers) who are at risk for NMUPO and these patients should be monitored closely by both caregivers and providers when given perioperative opioids.

Recommendation*:* A specific screening tool for NMUPO such as the CRAFFT tool should be utilized to follow teenagers who have been prescribed opioid medications following surgery associated with significant pain.

Strength of evidence: A

Perioperative management of patients with opioid addiction:

There are no controlled or observational studies that specifically address the issue of how to manage perioperative opioids in patients who have opioid addiction. At the same time, opioid maintenance treatment is being prescribed with increasing frequency for adolescents and young adults who misuse opioids. While methadone was previously the most commonly used medication, there has been rapid increase in prescribing of Suboxone®, a combination of buprenorphine and naloxone. The naloxone is added to deter misuse via injection of the combination; it has minimal impact when the combination is ingested sublingually. Buprenorphine is a long acting opioid that is a high affinity partial agonist at mu-receptors and an antagonist at kappa- and delta-receptors. Patients on opioid maintenance programs may be treated like patients with ongoing pain: opioid maintenance should be managed by the provider who has done so preoperatively. It is generally agreed that methadone and buprenorphine doses should be continued through the operative and recovery time periods. In the case of buprenorphine or Suboxone®, it should be noted that if additional opioids are needed to manage surgical pain, their effectiveness may be markedly impaired by co-administration of these medications.[114] For major surgery where opioid requirements are anticipated to be significant, a preoperative switch from buprenorphine/ Suboxone® to morphine or methadone maintenance has been recommended. Continuing on a previous opioid maintenance regimen versus switching to other agents is an area of current controversy. For individual patients, it requires practical consideration of their individual risk of relapse, social supports, and monitoring for over or under dosing during a conversion.

Patients that are misusing or abusing opioids should be referred to an addiction specialist. **Elective surgery should not be undertaken until appropriate management of addiction is assured.** When surgery cannot be delayed, patients should be given enough opioids for analgesia consistent with the degree of physiologic trespass. Perioperative management of former opioid addicts is based on common sense rather than prospective studies. A clear discussion needs to be held with the patient before the procedure regarding the goals for the anesthetic and analgesic plans. The risk of precipitating a return to addictive behaviors with perioperative opioid use needs to be elucidated.

***Recommendation*:** When caring for the patient with opioid addiction who is taking opioids chronically, optimize administration of non-opioid analgesia, including ketamine, alpha-adrenergic agents, local anesthetic/peripheral nerve blocks, acetaminophen, NSAID medications, and adjunctive neuropathic pain analgesics. If opioids are needed to provide adequate analgesia, they should not be withheld. Maintenance opioids should be continued throughout the perioperative timeframe. Upon discharge the patient should be given a defined weaning plan and only enough opioid to accomplish this wean. All of these patients should be referred to and managed by a pain physician when

possible. In some cases, an operation that is typically performed on an ambulatory basis should be considered for inpatient admission in order to provide optimal analgesia, e.g., a continuous peripheral nerve catheter, and monitoring during the time of most severe postoperative pain.

Strength of Evidence: C

Tools in appendix

Assessment of Pain and Analgesic Efficacy

There is wide agreement that appropriate assessment of pain is necessary in order to better guide care during the perioperative and postoperative period.[115-118] Unfortunately, there are insufficient data to support the beneficial effect of routine pain assessment on patient outcomes.[119] Furthermore, observational data evaluating institutional practices demonstrate inconsistencies in the frequency and nature of pain assessment in many hospital settings.[120-123] Inappropriate assessment and or misinterpretations of pain assessments may lead to under- or over-use of analgesics and suboptimal or even harmful outcomes.[124-126] Consensus documents addressing pain management in children recommend that assessment of a child's pain should be multi-dimensional (location, nature, intensity), developmentally guided, and include the use of well-established instruments (those with at least 2 peer reviewed studies by different teams that have established reliability and validity).[115-118] It is also recommended that pain assessments (including use and interpretation of pain intensity scores) be made in consideration of the unique situational context, e.g., type and nature of surgery, treatments received, and psycho-social factors.[127-129]

***Recommendation*:** Regular pain assessments should be part of the perioperative care/treatment of pediatric patients. These assessments should be made using validated measures. The pain assessment should take into account the unique circumstances of the patient's psychological state and the extent of surgery.

Strength of Evidence*:* B

Pain intensity:

Observational studies demonstrate that children ≥ 4 years of age can reliably use self-report instruments to report and score pain intensity. However, children less than 8 years have exhibited difficulty distinguishing between sensory pain, e.g., incisional pain, and distress or affect, e.g., fear,[118,130] and often exhibit scoring biases.[131] Additionally,

young children aged 4 to 8 have been observed giving differing pain scores to different people during a painful procedure.[132] There is insufficient evidence to know whether older children or adolescents exhibit scoring biases.

Systematic reviews and consensus panels have identified several self-report measures that are considered well established in measuring pain intensity during procedures, after surgery, and for use in clinical analgesic trials.[133,134] These include (but are not limited to) the 0-10 numeric rating scale (NRS), Faces Revised Pain Scale (FRPS), and the color analogue scale. It is widely recommended by consensus groups that a self-report of pain intensity be obtained whenever possible to assess and document the child's perceived level of pain intensity,[115,116,135] and that behavioral observation be used to complement self-report, particularly when scores are inconsistent with the clinical presentation, contextual factors, or appear to be biased.[115,126]

Several observational studies have reported average self-reported numeric, or faces pain intensity scores that children associate with perceptions of pain severity and their need for analgesia,i.e., in general, higher scores are more often associated with perceived need.[128] However, wide variability has been observed in children's pain perceptions and reported population averages may not reflect the needs of the individual child. Pain intensity scores must therefore be interpreted in context. For instance, studies that based titration of opioid doses on specific pain scores (most commonly to achieve a score of less than 4/10) have resulted in high rates of excessive sedation.[136] Thus, use of arbitrary pain intensity scores for titrating opioids may lead to over- or inappropriate use of opioids and has been deemed "risky and inappropriate" by many, including the Joint Commission.[137,138] Other, more global comfort and function outcomes (ability to deep breathe and cough, get out of bed, etc.) are more nebulous but better indicators of analgesic need compared to arbitrary target pain scores.

Recommendation: Pain intensity scores can be used to assess a child's perceived degree of discomfort. However, decisions to administer analgesics should take into consideration patient functional behaviors, situational factors such as pain source, self-reported pain scores, parental observation, and other potential sources of distress, rather than arbitrarily selected pain score cutpoints.[124,127,139]

***Strength of Evidence*:** B

Behavioral observation:

Behavioral observation instruments can be used reliably to document pain behaviors in children who cannot self-report, including those younger than 4 years, infants, neonates, and children or adolescents with moderate to severe cognitive impairments. Observational studies have demonstrated that behavioral observation instruments can

be used reliably between providers to document pain behaviors.[135,140,141] These measures include (but are not limited to):

- Behavior and posture related scales (Faces, Legs, Activity, Cry, Consolability (FLACC), Children's Hospital of Eastern Ontario Pain Scale (CHEOPS))
- Combined behavioral/physiologic parameter scales (Crying, Requires O2, Increased Vital Signs, Expression, Sleepless (CRIES))

Observational evidence also suggests that behavioral pain scores are moderately consistent with nurses' and parents' global assessments when assessing pain in children who cannot self-report. Observed pain behaviors correlate significantly but not consistently with children's self report.

There is insufficient evidence to support that behavioral observation instruments can differentiate pain distress from other sources of distress such as physiologic compromise or fear.[141,142] Thus, consensus publications recommend that behavioral observation measures be used to assess presence and intensity of pain in children who cannot self-report, but also that scores be interpreted with caution and in consideration of the situational context and other factors.

***Recommendation*:** Behavioral observation can be used to assess pain-related distress in children. Directions to administer analgesics in patients who cannot self-report should take into consideration situational factors such as pain source, observational pain scores, and other potential sources of distress, rather than arbitrarily selected pain score cut-offs.

***Strength of Evidence*:** B

Analgesic responsiveness:

Data from observational and clinical trials of analgesics have demonstrated that self-report and behavioral observation pain intensity scores are sensitive in detecting pain relief after analgesic administration and over time (i.e., scores decrease significantly after administration).[143-149] Observational studies have also reported "Mean Clinically Significant Differences", i.e. the average decrease in pain score that reflects perceived pain relief for children as young as 6 and 8 years.[146,150] On average, a decrease of 1 point on the 0-10 Numeric Rating Scale is associated with a child's perception of pain relief. However, the data show wide variability and inconsistencies in reporting, e.g., some scores go up when the child reports relief and these are not stable across pain intensity ratings.

***Recommendation*:** Changes in pain scores should be used in conjunction with other verbal/behavioral measures as indicators of pain relief and analgesic response, e.g., side effects, when making analgesic decisions.

***Strength of Evidence*:** B

Physiologic measures:

Although an acute pain insult can induce changes in physiologic vital sign parameters such as heart rate and blood pressure, observational data have shown that these changes are non-specific and poorly sensitive pain indicators.[151,152] Recent data have demonstrated relationships between a measure of the respiratory fluctuations in heart rate, i.e., analgesia nociception index [ANI], and observed FLACC scores in a small sample of children, suggesting that an objective, physiologic indicator of pain based on parasympathetic tone may be useful for children who cannot self-report pain. [153] Such data are relatively sparse, and it remains unknown whether clinical use of the ANI will aid in analgesic decision-making.

Recommendation: Physiologic parameters should be used to assess the child's nociceptive response when it is not possible to assess pain with more sensitive measures, e.g., when the child is anesthetized or is receiving neuromuscular blockers. It is recommended that other potential sources of physiologic distress, e.g., emotional distress, hypovolemia, fever, hypercarbia, be considered and/or ruled out when making treatment decisions.

***Strength of Evidence*:** B

Postoperative recovery and function:

Consensus opinion supports assessment of the child's physical *functioning* when assessing recovery from pain and surgery, yet there is insufficient evidence regarding valid or reliable measures to assess children's physical function related to acute postoperative pain.[135] Pain interference instruments categorize the degree to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. Observational data support the reliability of parental functional assessment of the child's pain interference after surgery.[154,155] Pain interference also incorporates items that address ability to sleep and school attendance. These tools are available for adults and pediatric self-reporters as well as a version where parents serve as proxy reporters.
(https://www.assessmentcenter.net/documents/PROMIS%20Pain%20Interference%20Scoring%20Manual.pdf)

***Recommendation*:** A child's functional recovery should be assessed at least globally, to inform treatment plans.

***Strength of Evidence*:** C

Nature and Location of Pain:

Observational studies have demonstrated that children as young as 4 years can reliably identify a pain location, i.e., body map, that is consistent with clinical findings.[156,157] Additionally, observational data suggest that children as young as 8 years of age can describe the quality and nature of pain using word lists and scales.[158]

***Recommendation*:** Assessing pain location is recommended to differentiate incisional pain from other potential sources of postoperative pain.

***Strength of Evidence*:** B

Recommendation: The nature of pain should be assessed to inform differentiation of pain type.

Strength of Evidence: B

Monitoring of Patients on Opioid Therapy

Because of variability in both efficacy and adverse effects of opioid analgesics among patients, the goals of monitoring patients on opioid therapy include:

1. Assessment of pain to ensure that patient has pain relief associated with the drug and modality employed and to guide titration of drug.
2. Monitoring (through technology and human observation) of vital signs and level of sedation to assess adverse effects of opioids, most importantly opioid related respiratory depression (ORRD), and other side effects from excessive sedation.

The American Society of Anesthesiologists (ASA), the Anesthesia Patient Safety Foundation (APSF), the Joint Commission, Centers for Medicare and Medicaid Services (CMS), and pain management advocacy organizations have promulgated practice guidelines incorporating the recommendations discussed below.[159-164] The American Pain Society has also published guidelines for management of postoperative pain in both adults and children.[165]

Physiologic monitoring:

There are no prospective randomized trials investigating the minimum monitoring requirements concerning pediatric patients on PCA opioid infusions. In addition, here are no clinical trials correlating levels of monitoring with significant adverse outcomes. In spite of this, a national survey of select members of the Society for Pediatric Anesthesia (SPA) members representing 252 institutions in the United States showed that 90% of pediatric anesthesiologists monitored patients on PCA with continuous pulse oximetry.[48] Consensus documents and expert opinion advise basic monitoring of respiratory and cardiovascular status to recognize hypoventilation and apnea particularly for those who are naïve to the drug and modality.[63,165-168] Experts agree that physiologic monitoring of pediatric patients receiving initial doses of parenteral opioids or opioids by PCA/NCA/PCA-P (parent and proxy) and/or constant infusion should include respiratory rate (by plethysmography or direct observation), and continuous pulse oximetry. It is important to remember that pulse oximetry is not an accurate monitor of adequacy of ventilation when supplemental oxygen is being administered. Capnography is a more sensitive modality in the identification of respiratory depression in this setting. At this time, capnography is not routinely recommended, although its use has been described [165,169,170] primarily in adults. To date, with current technology, capnography has been shown to be largely impractical in children in the post-operative setting.[167] New technologies are being developed to detect airway obstruction/hypopnea. These include respiratory volume monitoring[171] and detection of expired gas moisture or temperature. These modalities have not been tested or validated in children for monitoring of opioid use in the perioperative setting. Transcutaneous carbon dioxide monitoring may be useful to detect hypopnea. Several transcutaneous $PaCO_2$ monitors have been evaluated in pediatric populations [172] including a combined transcutaneous oximeter/carbon dioxide monitor which has been validated in children and low birth weight neonates .[173] Unfortunately none of these have been evaluated in infants and children receiving opioid medications (specifically) in the post-operative setting.

Observational studies indicate that patients with baseline cognitive dysfunction may have a higher risk of respiratory depression on conventional PCA doses.[14,57,174,175] In addition, patients who are managed on high opioid doses in the first 24 hours postoperatively may be at higher than average risk of respiratory events.[57]

***Recommendation*:** Physiologic monitoring of patients receiving initial opioid patient/nurse controlled analgesia [PCA/NCA/PCA-P (parent and proxy)], continuous infusion of opioid, or initial doses of opioid should include continuous monitoring of pulse oximetry. Continuous monitoring of RR and ECG should be considered in pediatric patients who are on oxygen, or who have specific risk factors for respiratory depression.

***Strength of Evidence**:* C

Recommendation: Patients who have been on stable doses of opioids via PCA, NCA, or PCA-P for more than 24 hours and who are alert, awake, may not require ongoing physiologic monitoring.

Strength of Evidence: C **-** based on expert panel opinion.

Recommendation**:** Patients with cognitive dysfunction or those receiving doses of opioids that are higher than normally recommended (in the first 24 hours postop) should be considered for enhanced continuous respiratory monitoring due to higher risk for hypoventilation and apnea.

Strength of Evidence: B

Observation of respiratory pattern and quality:

In addition to physiologic monitoring by technology, nursing assessment should be vigilant and include assessment of respiratory parameters other than rate. These include pattern (regularly spaced breaths vs. long or irregular pauses), depth, quality of effort (easy vs. labored), breath sounds (snoring, stridor, or stridor due to obstruction).

Equal vigilance should be employed for all pediatric patients receiving opioids in the postoperative period, regardless of modality ("as needed" nurse administered bolus, PCA, or PCA-P). Patients receiving intermittent nurse administered bolus opioid should be evaluated for change in pain score, respirations and level of sedation after bolus administration to assess individualized response and appropriateness/efficacy of the ordered dose. If pain relief is inadequate, continued scrutiny is warranted after dose increases and/or the addition of a basal opioid infusion to PCA. Meta-analysis of adult studies has shown risk of respiratory depression to be similar between as needed bolus administration of opioid and PCA bolus administration.[176]

Extra vigilance is recommended in populations at increased risk for respiratory depression and/or airway obstruction from opioid and/or sedative administration. These populations include:

1. Neonates (because of immaturity of respiratory control mechanisms as well as drug metabolism and clearance)
2. Cerebral palsy (poor coordination of airway musculature, increased secretions)
3. Neuromuscular diseases (weakness of muscles of respiration (chest wall) and airway musculature)
4. Cognitive impairment (difficult assessment of pain, sedation, level of consciousness)
5. Sleep disordered breathing and obstructive sleep apnea patients (related to anatomic abnormalities such as Pierre-Robin, obesity, tonsil-adenoid hypertrophy)
6. Poly-pharmacy (co-administration of benzodiazepines and/or sedatives)[177,178]

7. After increase in PRN bolus dose or PCA dose of opioid, or addition of basal infusion rate to PCA
8. Opioid naïve patients (particularly on the first post-operative night).
9. Patients on supplemental oxygen (which impairs the sensitivity and response time of pulse oximetry as a monitor for apnea/hypopnea)
10. Patients receiving neuraxial opioids.

***Recommendation*:** Frequent assessment of the quality as well as the rate of respiration should be performed by direct observation and recorded in the medical record. Increased frequency and intensity of these observations is recommended for patients in high-risk groups in addition to standard electronic monitoring.

Strength of Evidence: C

Sedation Monitoring:

Excessive sedation has been found to predict/precede opioid related respiratory depression and was observed prior to opioid-related death/neurological injury in a majority of children.[179] Patients receiving PCA or PCA-P with or without a basal infusion should, therefore, be monitored for their level of sedation. Sedation scales developed and validated for use in patients undergoing procedural sedation, such as the Ramsey Scale or the University of Michigan Sedation Scale (UMSS) that *only* include immediate response to commands or physical stimulation may be less appropriate than a scale such as the Pasero Opioid Sedation Score (POSS). Although not tested in the clinical pediatric or adult settings, the POSS is a logical tool to assess the opioid-related sedation effect in that it requires the patient to have a conversation with the rater and determines whether somnolence causes the patient to fall asleep during conversation.[178] The POSS also includes suggested measures to respond to moderate (reduce opioid dose and observe) to excessive sedation (stop the opioid, administer naloxone). It should be noted that all of these scales require that the rater stimulate the patient and subsequently evaluate respiratory rate, depth and pattern. Respiratory evaluation needs to be done before stimulating the patient since measures after patient stimulation are inaccurate.

***Recommendation*:** Patients receiving opioid analgesia perioperatively should have regular assessment of their level of sedation using a validated sedation score that evaluates level of alertness or mentation rather than utilizing a procedural sedation scale. This rating should be part of the medical record for monitoring.

Strength of Evidence: B

Institutional surveillance/safety review for opioid-related adverse events:

Surveillance for opioid related adverse events has been recommended, including regular review of rapid response team and/or code team calls as well as the need for naloxone administration. Publications of such institutional review procedures provide information regarding risk for adverse events in both adults and children.[166,180,181] Sophisticated filtering of physiologic monitoring data has been reported to detect prevalence of hypoxia in patients receiving opioids.[182] Importantly, concerns have recently been raised about the contribution of "alarm fatigue" to failure to rescue with respect to opioid overdose.[183]

***Recommendation*:** Review of Code Team calls or emergency response calls, and the delivery of emergent naloxone doses should be part of institutional efforts to critically evaluate and reduce preventable opioid-related adverse events.

***Strength of evidence*:** B

Opioid Side Effects in Children

Children may experience important side effects from opioid analgesics, including: respiratory depression and sedation, tolerance, hyperalgesia, nausea/vomiting, pruritus, chest wall rigidity, and potential long-term effects from short-term use.[184,185] In the perioperative period, these potential complications are particularly troublesome, as the doses of opioids required for pain management are generally much higher than at other times during a patient's hospitalization.

Stratification of risk for opioid side effects is an emerging field within pain management and perioperative medicine. Recent studies of risk predictors of opioid-related adverse events include determinations of genetic predisposition,[186,187] and variability in pain management according to ethnicity.[188]

Respiratory adverse events related to opioid administration:

Respiratory depression is the most feared adverse event related to opioid administration in pediatric patients. It has been found to have an incidence of 0.4% in young patients (average age of 2.5 years) in an audit of Nurse Controlled Analgesia (NCA) in a children's hospital.[59] This overall rate was further elucidated to be 2.5% in neonates, and 0.27% in those over 1 month. An audit of opioid infusions from the United Kingdom found the rate of significant respiratory events was 0.13%[168], with rates of significant respiratory depression in infants less than 1 year also higher, at 0.3-0.4%.

Brown et al (2006)[189] prospectively studied the effects of pediatric recurrent hypoxemia on sensitivity to the respiratory depressant effects of morphine in 20 children with obstructive sleep apnea. Having previously determined an increased risk in those with a nighttime oxygen saturation nadir of <85%[87], the patients were grouped into severe or moderate sleep apnea. Those with severe obstructive sleep apnea as measured by low oxygen nadir were more sensitive to morphine respiratory depression and required lower total dose of morphine for pain management post tonsillectomy than those with mild sleep apnea. The increased risk of postoperative respiratory depression is also seen in adult sleep apnea.[190]

Some adverse respiratory events may be traced to inaccurate dosing due to obesity. Specifically, opiate dosing based on total body weight can result in dangerous respiratory depression. [191,192] Dosing should be based on ideal, or lean body mass which can be calculated using one of many dosing scalers rather than rough estimates of appropriate weight dosing.[193]

Recommendation: Serious adverse respiratory events are not common with opioid use in children, but the incidence is higher for patients under 1 month age and in those with comorbidities. More intensive monitoring is indicated for these populations (See Monitoring Section above).

Strength of Evidence: B

Recommendation: Patients with obstructive sleep apnea, obesity (>95 percentile) and recurrent night time oxygen desaturations are at higher risk for opioid induced respiratory depression and should have their dose of opioid reduced by 50 to 67% in addition to requiring additional monitoring in the perioperative period when opioids are being administered. [193]

Strength of Evidence: B

Recommendation: Morbidly obese patients should not have opioid dosing based on total body weight but rather based on ideal or lean body mass in order to avoid respiratory depression.

Pruritus:

Opioid-induced pruritus is a common problem, with incidences between 2 and 10% for intravenous morphine. The mechanism is not understood, but central mu-receptor activity likely has an important influence. In the case of morphine, histamine and mast cell mediator release may affect peripheral receptors. Studies of treatment of opioid-induced pruritus have been limited, particularly for intravenously-administered opioids. Most notable is a randomized controlled trial of 184 children greater than 7 years old

treated with patient-controlled analgesia, given 50 mcg/kg of nalbuphine for itch. The authors found no benefit of nalbuphine.[194] Nevertheless, a systematic review of ten studies found overall benefit of nalbuphine for treatment of opioid-induced pruritus.[195]

Naloxone has a mixed track record in pediatric perioperative care. West found no effect on itch in a randomized controlled pediatric trial of naloxone/morphine admixture in patient-controlled analgesia.[196] On the other hand, a randomized controlled trial with naloxone infusion given to children separately from the patient-controlled intravenous morphine, in a dose finding study, Monitto and colleagues[197] found naloxone to be effective for treatment of itch in over 90% of cases at a dose of 1 mcg/kg/h, without reversing analgesia or increasing required morphine doses. A randomized controlled trial of 46 pediatric patients using postoperative PCA found less pruritus with low-dose (0.25 mcg/kg/hr) naloxone infusion than placebo and that pain control was not adversely affected.[198]

Recommendation: Naloxone infusion is helpful in treating and possibly preventing opioid-induced pruritus. There is insufficient evidence to support the use of nalbuphine in children for intravenous opioid-induced pruritus at this time.

Level of evidence*:* A (Naloxone)

Emesis:

There are many studies of perioperative nausea and vomiting in children, but few evaluating the effect of opioid on the incidence of perioperative nausea and vomiting in particular. Most of these have been studies in surgical populations with a high incidence of such as tonsillectomy and adenoidectomy or strabismus surgery. Perioperative opioids are known to increase postoperative nausea and vomiting when compared to non-steroidal anti-inflammatory drugs.[199] [200] The magnitude of this effect varies with the type of surgery performed, anesthesia used, and patient population studied. Moiniche reported nausea and vomiting as a secondary endpoint in a systematic review of NSAIDs compared to opioid for tonsillectomy analgesia. The use of NSAIDs significantly improved nausea and vomiting when compared to opioid. This finding is consistent in several other studies of perioperative opioid use in children.[201-204] Conversely, in a prospective, randomized controlled trial of children given a propofol-based anesthetic and dexamethasone for nausea and vomiting prophylaxis, Keidan compared ketorolac to fentanyl [205] and found no appreciable difference in postoperative nausea and vomiting in children (baseline rate was much lower). Double-blind, randomized, controlled trials show that the choice of anesthetic technique, the surgical procedure, and pharmacological prophylaxis affect the incidence of postoperative nausea and vomiting specifically related to intraoperative opioid use[206-211] as do lower morphine doses.[212] Eberhart and colleagues[213] evaluated the contribution of opioids to perioperative nausea/vomiting in a meta-analysis of propofol vs. inhaled agents for

maintenance of anesthesia. This group did not find that intraoperative opioids increased the risk of postoperative nausea and vomiting. Another systematic review [214] of 13 randomized controlled pediatric trials of morphine compared to placebo or active control found that morphine had a significantly greater incidence of nausea than the active controls, including nerve blocks, tramadol, buprenorphine, and ketorolac.

In similar (in some instances the same) studies as mentioned for investigation of pruritus, the use of low-dose continuous naloxone infusion has been studied for the prevention of nausea and vomiting. A randomized controlled trial of pediatric patients using postoperative PCA found less nausea with 0.25 mcg/kg/hr naloxone infusion when compared to placebo. A dose finding study involving 59 pediatric patients found that infusion rates greater than or equal to 1 mcg/kg/hour led to significantly less nausea than lower infusion rates.[215] As mentioned above, when used in low doses, naloxone has not been shown to significantly affect pain control or opioid usage.[198,215] Several other medications such as transdermal scopolamine,[216] 5-HT3 receptor antagonists (i.e. tropisetron,[217] ondansetron,[218] ramosetron[218]), and dixyrazine[219] have also been shown to decrease the incidence of nausea and vomiting for postsurgical patients utilizing PCA opioids for analgesia. Each of these agents has a small risk of causing other side effects. In particular, agents with anticholinergic and antihistaminic actions contribute to postoperative delirium, sedation, and bowel and bladder dysfunction. Nalbuphine has been found to be ineffective in pediatric patients for PCA-related nausea and vomiting.[220]

***Recommendation*:** Naloxone infusion should be considered for patients on opioid PCA therapy for the prevention or treatment of nausea, vomiting.

Strength of Evidence: A

***Recommendation*:** It is reasonable to consider common anti-emetic medications (5-HT3 receptor antagonists, antipsychotics, anticholinergics) for the treatment or prevention of nausea and vomiting while on opioid PCA therapy.

Strength of evidence: A

Chest wall rigidity:

Chest wall rigidity has the potential to delay effective ventilation. It appears that the complication known in the literature as “chest wall rigidity” is actually a combination of glottis closure and chest wall rigidity, which is affected by dose, speed of delivery of the dose, potentially the age of the child and with the incidence varying from opioid to opioid. There are case reports [221] and a prospective observational case series of chest wall rigidity associated with fentanyl and remifentanil administration in children [222] which found an association with the speed of opioid delivery. In a prospective study in

30 adults, Bennett [223] showed a potential contribution of glottic closure contributing to difficult ventilation with 3 mcg/kg of sufentanil. There are also case reports of perinatal chest rigidity after mothers received remifentanil or fentanyl during cesarean section.[224,225] In adults, the ventilatory difficulties appear to be related to dose and speed of delivery, even lower doses of fentanyl (2 mcg/kg) have been associated with this side effect.[226] Fentanyl and remifentanil-associated chest wall rigidity have been the subject of comparative studies in the neonatal intensive care unit.[227] Choong in 2010 compared remifentanil 3 mcg/kg IV over 60 seconds with 2 mcg/kg fentanyl and succinylcholine for intubation in the neonatal intensive care unit. They found chest wall rigidity to occur at a rate of 2 out of 15 patients, but these patients had no co-induction agents.

Recommendation: Rapid intravenous administration of certain opioids are associated with chest wall rigidity and possibly glottic closure, particularly in infants and neonates within the pediatric age ranges. There is a greater association with the synthetic opioids and younger age. Muscle relaxation and co-induction agents appear to reduce or eliminate the development of chest wall rigidity.

Strength of Evidence*:* B

Pain Sensitization after Pain Exposure and Opioid administration:

Pain sensitization remains an area of intense interest when considering opioid adverse effects. Peters et. al.Peters, Schouw [228] found increased pain sensitivity in later life in a long-term follow-up study of neonates in the intensive care unit. Other long-term follow-up studies in neonatal intensive care patients, have suggested there may be long-term effects on neurodevelopment with the use of opioids. In these infants pain and stress treated with opioids were associated with altered behavioural and endocrinologic outcomes - with both fentanyl and morphine implicated.[229-232,233]

Recommendation: Exposure to pain and stress in infants may have important long-term consequences. The effect of opioids in mitigating or exacerbating these outcomes is uncertain and needs further elucidation. Avoiding opioid exposure when possible by choosing other analgesic strategies is prudent.

Strength of Evidence: B

Tolerance/Hyperalgesia:

Tolerance and/or hyperalgesia are major side effects that have long been associated with the use of opioids in children and adults. These twin problems have recently become more prominent with the use of the ultra-short acting opioid remifentanil. Crawford, Hickey [234,235] compared remifentanil infusion throughout surgery with

morphine at emergence to morphine infusion throughout surgery in adolescent patients undergoing scoliosis repair in a randomized controlled trial. The remifentanil group had increased postoperative PCA opioid requirements in the first 24 hours. Compelling case reports have also described hyperalgesia after remifentanil infusion.[235] Similar studies have suggested the development of tolerance and hyperalgesia to remifentanil appears to be dose related, with higher doses (0.6-0.9 mcg/kg/min) associated with a higher incidence of acute tolerance.Kim, Lee [236] Pharmacokinetic data on hyperalgesia in chronic pain indicate that there is a "peak effect" profile, rather than a linear hyperalgesic/tolerance effect. Numerous adult studies support remifentanil-induced hyperalgesia and/or acute tolerance at higher doses (>1 mcg/kg/min) as evidenced by the systematic reviews by Kim, Fletcher, and Hood.[237],[238,239] There is also a suggestion of an increased incidence of hyperalgesia in patients also receiving inhalational anesthetics rather than intravenous anesthesia. Although these data are almost exclusively collected in adult patients, these concerns are applicable to adolescents that are treated by pediatric anesthesiologists.

The literature regarding neonatal hyperalgesia less clear. Roulleau, Gall [240] in a randomized, open label, prospective, study, compared remifentanil (variable doses) to sufentanil in neonates and infants undergoing cleft lip and palate surgery.[207] They found no hyperalgesia in the remifentanil group who were given morphine 30 min prior to end of surgery. On the other hand, Hallett reported a case of morphine/fentanyl induced hyperalgesia in an infant following multiple surgeries with increasing infusion dose requirements.[241] In a study of short-term opioid infusion in 24 neonates in the critical care unitWelzing, Link [242] the response to remifentanil infusions compared to fentanyl infusions was investigated and no evidence of opioid-induced hyperalgesia was found.[209]

Two prospective, randomized controlled single-center trials studied the prevention of tolerance or hyperalgesia in children in the perioperative setting. Ketamine bolus and infusion throughout surgery[243] and morphine as a single doseMcDonnell, Zaarour [244] have not been shown to be protective. Adult studies have suggested that ketamine infusion during surgery improves pain scores and decreases opioid requirements, suggesting a role in decreasing hyperalgesia and/or tolerance.

***Recommendation**:* There is evidence to support the existence of acute opioid tolerance in adults and adolescents. Remifentanil-associated acute tolerance and/or hyperalgesia appears to be dose related. Remifentanil dose should be used with the awareness of acute hyperalgesia or tolerance - particularly in adolescents during major surgery. There is insufficient evidence to support the existence of acute opioid tolerance associated with opioids other than remifentanil.

***Strength of evidence**:* B

Recommendation: There is insufficient evidence to recommend specific techniques for the prevention of opioid induced hyperalgesia in children when used in the perioperative setting. The literature suggests intermediate -acting opioids or adjuncts should be administered at the end of surgery to avoid immediate discomfort in patients treated with remifentanil. The protective effect of ketamine is uncertain.

Strength of evidence: C

The Impact of Adjunctive Medications on Opioid Dosing and Side Effects in Perioperative Children

The opioid sparing effect of NSAIDS and acetaminophen:

Opioid dose reduction has been studied with the use of acetaminophen and NSAIDs. Wong and colleagues [245] found 38 randomized controlled trials comparing NSAIDs or paracetamol vs. placebo and showed a clear decrease in opioid dose with the use of NSAIDs in most studies, and improved pain scores. Less clear was the amelioration of opioid-related side effects. Michelet[246] performed a meta-analysis of randomized controlled trials of NSAIDs on the incidence of postoperative nausea and vomiting, pain scores and opioid consumption. They found 27 articles, which together showed a decrease in opioid consumption in the postanesthetic care unit, a decrease in pain scores in the first 24 hours, and a decrease in opioid consumption and nausea and vomiting in the first 24 hours.

Acetaminophen is likely to decrease the opioid requirement, particularly when administered intravenously.[12,74] Rectal dosing of acetaminophen may not be as effective,[247] but the dose employed is critical when considering this route of administration due to poor and variable absorption.[248] Morton found 20 mg/kg intraoperatively, followed by 15 mg/kg q6 hourly to be ineffective in reducing opioid dosing by PCA.[248] Other investigators have shown that a loading dose of 40mg/kg followed by 20mg/kg every 6 hours is required in order to maintain adequate blood levels for clinical effect, and that the time to attain these levels is between 90 and 180 minutes.[249] Further consideration must be given to the fact that rectal dosing results in varied blood levels,[247] and may contribute to the drugs lack of efficacy in some studies. The translation of decrease in opioid dose to a decrease in opioid-related side effects is less obvious. An adult systematic review of 30 studies suggests an improvement in nausea and vomiting through superior pain control with intravenous acetaminophen added to an opioid regime.[250]

In a random effects meta-analysis examining 85 pediatric studies that included acetaminophen and NSAID related opioid-sparing effects, Kossowsky reported on the distributions of pain scores in study and control groups and relationships between

opioid sparing and pain scores. For both NSAIDS and acetaminophen, a significant opioid sparing effect was demonstrated in the vast majority of studies by several measures including total dose used, percentage of children requiring rescue medication, and time to first rescue medication. Pain scores were also lower in the treatment cohorts.[251]

Recommendation: NSAIDs are appropriate opioid sparing agents and have been shown to decrease nausea and vomiting perioperatively. Where appropriate, they should be administered to reduce or eliminate the need for opioids and decrease nausea and vomiting after surgery.

Evidence: A

Recommendation: Acetaminophen is opioid sparing in the perioperative period. Where appropriate it should be administered to reduce or eliminate the need for opioids and decrease nausea and vomiting after surgery.

Strength of Evidence: Intravenous acetaminophen = A. Oral and rectal =B

The effect of ketamine on opioid sparing:

Four randomized controlled trials examined the question as to whether or not intraoperative a ketamine bolus and/or infusion can decrease opioid consumption and side effects in children. A study of 75 children post-appendectomy showed no improvement in morphine consumption but a greater need for opioid rescue and side effects in the cohort that received ketamine.[252] A study of 30 children after urological surgery showed no difference between those who did and did not receive ketamine,[253] as did another study of 34 children after scoliosis surgery.[243] One study of 50 children after scoliosis surgery who received both ketamine and magnesium intraoperatively showed decreased morphine consumption, and improved sleep and pain scores in the first 24 hours after surgery.[254] Other studies have examined the analgesic effects of postoperative infusions of ketamine. Two studies of patients after thoracoscopic pectus excavatum repair (Nuss procedure), one with 60 patients and the other with 44 patients, both showed decreases in opioid equivalents and side effects in the cohort receiving ketamine.[255,256] In contrast, a third study of 54 patients after scoliosis surgery showed no difference in PCA use, pain scores or side effects in patients that received a 72-hour postoperative ketamine infusion as compared to placebo.[257] An additional randomized controlled study compared morphine consumption after scoliosis surgery in 48 adolescents who had a 72-hour low-dose ketamine infusion to those who did not found no difference in morphine utilization or in the secondary endpoints including pain, sedation, and undesirable effects.[258]

In a meta-analysis of ketamine for perioperative pain management in children, Dahmani et. al. [259] determined that ketamine was associated with decreased PACU postoperative pain intensity and non-opioid analgesic requirement, but only in the PACU, not in later pain outcomes. Likewise, Cho et. al. [260] found that preoperative administration of ketamine, either systemically or locally, provided equivalent pain relief to opioids and decreased analgesic requirements, but only in the first 24 hours, with no significant difference between ketamine and control groups for adverse effects. A systematic review of the literature of perioperative ketamine in adults determined that low-dose ketamine infusion (less than 1.2 mg/kg/h) reduced opioid consumption by an average of 40% in the postoperative period.[261] Also in adults, a meta-analysis[262] of 36 randomized controlled trials, most of which had low risk of bias, showed reduced PCA opioid requirements, as well as decreasing postoperative nausea and vomiting.

Recommendation: Perioperative ketamine has an intraoperative opioid sparing effect and in the immediate postoperative setting. There is insufficient evidence to support any effect on longer-term pain outcomes in pediatric-aged patients.

Evidence: A

Dexmedetomidine effect on opioid consumption:

Given the alpha-2 agonist effect on pain modulation, some researchers have suggested that dexmedetomidine could help decrease the requirement for pain medication in the post-operative time frame. Two retrospective studies found no improvement in postoperative pain or reduced opioid consumption for intraoperative dexmedetomidine.[263,264]

***Recommendation*:** The use of intraoperative dexmedetomidine is not recommended as an adjunct to PCA for pediatric perioperative pain control.

***Strength of Evidence*:** B

Gabapentin effect on opioid consumption and side effects:

One study of pre- and post-operative gabapentin in 59 teenagers after spinal fusion compared to placebo showed a reduction in PCA opioid consumption and pain scores, but no change in opioid related side effects.[265] A separate investigation found that a single dose of gabapentin compared to placebo did not improve pain scores or reduce PCA opioid consumption in a group of 44 adolescents after spinal fusion surgery.[266] One randomized controlled study showed a small benefit of improved pain control, reduced opioid consumption, and/or reduced opioid side effects with the perioperative use of gabapentin.

***Recommendation*:** There is conflicting and inconclusive data concerning perioperative gabapentin in patients as an adjunct to PCA for pediatric perioperative pain control.

***Strength of Evidence*:** A

The effect of intravenous lidocaine on opioid sparing:

Lidocaine has recently been used in the operating room for perioperative pain management. Although there is no literature on the use of perioperative intravenous lidocaine in children, there have been multiple meta-analyses and systematic reviews in adults showing opioid sparing in the early postoperative period and decreased nausea after abdominal surgery.[267-271] Kranke's systematic Cochrane review found moderate evidence of systemic lidocaine decreasing perioperative opioids, improving postoperative nausea and improving pain in the early postoperative period. Unfortunately, the studies included small sample sizes and a low risk of bias in only 20% of included studies.

Recommendation: Lidocaine may be helpful in providing a small opioid sparing effect. It may also reduce nausea and vomiting in abdominal surgeries .

Strength of Evidence: C (extrapolation from adult studies)

The effect of dexamethasone on opioid related side effects:

Dexamethasone has been widely studied in children. Shen and colleagues performed a systematic review of 13 articles investigating dexamethasone, ondansetron, or their combination in pediatric strabismus surgery and found a significant reduction in postoperative vomiting compared to placebo for each, and their combination more than either alone.[272] Conversely, Sinha did not find benefit to adding dexamethasone to granisetron in a randomized controlled trial of 136 children undergoing strabismus repair.[273] Steward and colleagues performed a systematic review and found that dexamethasone decreased postoperative nausea and vomiting in tonsillectomy, and that it also decreased postoperative pain.[274] In terms of steroid choice, Aouad compared dexamethasone with methylprednisolone for vomiting post tonsillectomy in children, and found 2.5 mg/kg of methylprednisolone to be non-inferior to 0.5 mg/kg of dexamethasone.[275] DeOliveira published a meta-analysis of 24 trials of dexamethasone in adults, finding that doses over 0.1 mg/kg IV decreased pain and opioid requirements after major surgery.[276] This study was updated 2 years later to include 60 trials and showed a dose of 4 to 5 mg decreased postoperative nausea and vomiting for 24 hours.[277] In children, Kim et. al. studied a range of doses of dexamethasone with respect to antiemetic effect and analgesic outcomes. They found no difference between cohorts in terms of emesis or pain in those who received 0.0625 and 1.0 mg/kg. [278]

Recommendations: In patients receiving perioperative opioids, dexamethasone administration can be helpful in decreasing postoperative nausea and vomiting, particularly after tonsillectomy and strabismus surgery. It is also recommended to decrease postoperative pain in tonsillectomy.
Note: Number needed to treat for effect may be higher when dexamethasone considered in the setting of the administration of a 5HT3 blocker such as ondansetron or granisetron.

Evidence: ***A*** (for postoperative nausea and vomiting), ***B*** (for pain), ***B*** (for dose).

Race and gender influences on adverse outcomes:

Recent studies of risk predictors of opioid-related adverse events include genetic factors or predisposition, variability in pain and opioid responsiveness.[186,187] In a prospective study of healthy children in a single institution in the United States undergoing tonsillectomy and adenoidectomy,[188] the authors studied race and variability in pain management. Despite a standardized anesthetic and surgical technique and standardized postanesthetic care unit pain management, they discovered an unequal burden of pain with African-American children experiencing higher levels. At the same time Caucasian children had greater number and severity of opioid-related adverse effects (with the exception of respiratory depression). In another prospective cohort study of latino and white non-latino children undergoing tonsillectomy, Jimenez et. al. found a higher incidence of side effects in Latino children[279].
Concerning gender influences, Sadhasivam[280] found that females had a higher incidence of opioid-related adverse effects, including nausea and vomiting, when compared to males in a prospective observational study of post-tonsillectomy and adenoidectomy pain treated with morphine.

Recommendations: There are genetically determined risk factors for vulnerability to opioid-related adverse effects. There is insufficient evidence to determine the influence of race or gender on treatment, expression of pain, experience of pain and side effects.

Strength of Evidence: C

Use of multimodal analgesic techniques to reduce opioid-related adverse events:

There is preliminary evidence that protocol-driven multimodal pain management strategies which include regional analgesic techniques and/or non-opioid analgesics may be associated with reduced risk of serious opioid-related adverse events in postoperative children.[181] A full review of the effectiveness of central and peripheral nerve blocks on opioid consumption is beyond the scope of this document and these recommendations, but there is a wealth of evidence (in both the adult and pediatric literature) that inclusion of appropriate regional anesthesia techniques (central or

peripheral) can decrease the total opioid requirement for perioperative patients during the duration of nerve block or infusion. [281-285] Other studies have further shown that peripheral nerve blocks can decrease adverse effects such as nausea and vomiting largely through their effect on decreasing opioid requirement. [286]

Recommendation: Multimodal pain management (including neural blockade) should be considered part of the perioperative analgesia plan for patients with significant painful stimuli in order to minimize the administration of opioid medication.

Strength of evidence: A

References:

1. Taddio A, Goldbach M, Ipp M, Stevens B, Koren G. Effect of neonatal circumcision on pain responses during vaccination in boys. Lancet 1995;345:291-2.
2. Anand KJ, Coskun V, Thrivikraman KV, Nemeroff CB, Plotsky PM. Long-term behavioral effects of repetitive pain in neonatal rat pups. Physiol Behav 1999;66:627-37.
3. Mattos JL, Robison JG, Greenberg J, Yellon RF. Acetaminophen plus ibuprofen versus opioids for treatment of post-tonsillectomy pain in children. Int J Pediatr Otorhinolaryngol 2014;78:1671-6.
4. Olkkola KT, Maunuksela EL, Korpela R, Rosenberg PH. Kinetics and dynamics of postoperative intravenous morphine in children. Clinical pharmacology and therapeutics 1988;44:128-36.
5. Wang C, Sadhavisvam S, Krekels EH, et al. Developmental changes in morphine clearance across the entire paediatric age range are best described by a bodyweight-dependent exponent model. Clinical drug investigation 2013;33:523-34.
6. Admiraal R, van Kesteren C, Boelens JJ, Bredius RG, Tibboel D, Knibbe CA. Towards evidence-based dosing regimens in children on the basis of population pharmacokinetic pharmacodynamic modelling. Archives of disease in childhood 2014;99:267-72.
7. Bhat R, Chari G, Gulati A, Aldana O, Velamati R, Bhargava H. Pharmacokinetics of a single dose of morphine in preterm infants during the first week of life. The Journal of pediatrics 1990;117:477-81.
8. Scott CS, Riggs KW, Ling EW, et al. Morphine pharmacokinetics and pain assessment in premature newborns. The Journal of pediatrics 1999;135:423-9.
9. Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. British journal of anaesthesia 2004;92:208-17.
10. Knibbe CA, Krekels EH, van den Anker JN, et al. Morphine glucuronidation in preterm neonates, infants and children younger than 3 years. Clin Pharmacokinet 2009;48:371-85.
11. Krekels EH, DeJongh J, van Lingen RA, et al. Predictive performance of a recently developed population pharmacokinetic model for morphine and its

metabolites in new datasets of (preterm) neonates, infants and children. Clin Pharmacokinet 2011;50:51-63.
12. Ceelie I, de Wildt SN, van Dijk M, et al. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. JAMA 2013;309:149-54.
13. Lynn A, Nespeca MK, Bratton SL, Strauss SG, Shen DD. Clearance of morphine in postoperative infants during intravenous infusion: the influence of age and surgery. Anesthesia and analgesia 1998;86:958-63.
14. Taylor J, Liley A, Anderson BJ. The relationship between age and morphine infusion rate in children. Paediatric anaesthesia 2013;23:40-4.
15. Greeley WJ, de Bruijn NP. Changes in sufentanil pharmacokinetics within the neonatal period. Anesthesia and analgesia 1988;67:86-90.
16. Gauntlett IS, Fisher DM, Hertzka RE, Kuhls E, Spellman MJ, Rudolph C. Pharmacokinetics of fentanyl in neonatal humans and lambs: effects of age. Anesthesiology 1988;69:683-7.
17. Davis PJ, Killian A, Stiller RL, Cook DR, Guthrie RD, Scierka AM. Pharmacokinetics of alfentanil in newborn premature infants and older children. Developmental pharmacology and therapeutics 1989;13:21-7.
18. Ross AK, Davis PJ, Dear Gd GL, et al. Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. Anesthesia and analgesia 2001;93:1393-401, table of contents.
19. Lynn AM, Nespeca MK, Opheim KE, Slattery JT. Respiratory effects of intravenous morphine infusions in neonates, infants, and children after cardiac surgery. Anesthesia and analgesia 1993;77:695-701.
20. Hertzka RE, Gauntlett IS, Fisher DM, Spellman MJ. Fentanyl-induced ventilatory depression: effects of age. Anesthesiology 1989;70:213-8.
21. Gill AM, Cousins A, Nunn AJ, Choonara IA. Opiate-induced respiratory depression in pediatric patients. The Annals of pharmacotherapy 1996;30:125-9.
22. Ballantyne JC, Carr DB, Chalmers TC, Dear KB, Angelillo IF, Mosteller F. Postoperative patient-controlled analgesia: meta-analyses of initial randomized control trials. J Clin Anesth 1993;5:182-93.
23. Berde CB, Lehn BM, Yee JD, Sethna NF, Russo D. Patient-controlled analgesia in children and adolescents: a randomized, prospective comparison with intramuscular administration of morphine for postoperative analgesia. The Journal of pediatrics 1991;118:460-6.
24. Walson PD, Graves PS, Mortensen ME, Kern RA, Torch MA. Patient-controlled versus conventional analgesia for postsurgical pain relief in adolescents. Developmental pharmacology and therapeutics 1992;19:32-9.
25. Shin D, Kim S, Kim CS, Kim HS. Postoperative pain management using intravenous patient-controlled analgesia for pediatric patients. J Craniofac Surg 2001;12:129-33.
26. Kotzer AM, Foster R. Children's use of PCA following spinal fusion. Orthop Nurs 2000;19:19-27; quiz 8-30.
27. Ellis JA, Blouin R, Lockett J. Patient-controlled analgesia: optimizing the experience. Clin Nurs Res 1999;8:283-94.

28. Petrat G, Klein U, Meissner W. On-demand analgesia with piritramide in children. A study on dosage specification and safety. Eur J Pediatr Surg 1997;7:38-41.
29. Till H, Lochbuhler H, Lochbuhler H, Kellnar S, Bohm R, Joppich I. Patient controlled analgesia (PCA) in paediatric surgery: a prospective study following laparoscopic and open appendicectomy. Paediatric anaesthesia 1996;6:29-32.
30. Beaulieu P, Cyrenne L, Mathews S, Villeneuve E, Vischoff D. Patient-controlled analgesia after spinal fusion for idiopathic scoliosis. Int Orthop 1996;20:295-9.
31. Petros JG, Mallen JK, Howe K, Rimm EB, Robillard RJ. Patient-controlled analgesia and postoperative urinary retention after open appendectomy. Surg Gynecol Obstet 1993;177:172-5.
32. Tobias JD, Baker DK. Patient-controlled analgesia with fentanyl in children. Clin Pediatr (Phila) 1992;31:177-9.
33. Gureno MA, Reisinger CL. Patient controlled analgesia for the young pediatric patient. Pediatr Nurs 1991;17:251-4.
34. Tyler DC. Patient-controlled analgesia in adolescents. J Adolesc Health Care 1990;11:154-8.
35. Lawrie SC, Forbes DW, Akhtar TM, Morton NS. Patient-controlled analgesia in children. Anaesthesia 1990;45:1074-6.
36. Webb CJ, Stergios DA, Rodgers BM. Patient-controlled analgesia as postoperative pain treatment for children. J Pediatr Nurs 1989;4:162-71.
37. Rauen KK, Ho M. Children's use of patient-controlled analgesia after spine surgery. Pediatr Nurs 1989;15:589-93, 637.
38. Gaukroger PB, Tomkins DP, van der Walt JH. Patient-controlled analgesia in children. Anaesth Intensive Care 1989;17:264-8.
39. Rodgers BM, Webb CJ, Stergios D, Newman BM. Patient-controlled analgesia in pediatric surgery. J Pediatr Surg 1988;23:259-62.
40. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248-73.
41. McNicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. The Cochrane database of systematic reviews 2015;6:Cd003348.
42. Faerber J, Zhong W, Dai D, et al. Comparative Safety of Morphine Delivered via Intravenous Route versus Patient-Controlled Analgesia Device for Pediatric Inpatients. J Pain Symptom Manage 2017.
43. Vetter TR. Pediatric patient-controlled analgesia with morphine versus meperidine. J Pain Symptom Manage 1992;7:204-8.
44. Jylli L, Lundeberg S, Langius-Eklof A, Olsson GL. Comparison of the analgesic efficacy of ketobemidone and morphine for management of postoperative pain in children: a randomized, controlled study. Acta Anaesthesiol Scand 2004;48:1256-9.
45. Ozalevli M, Unlugenc H, Tuncer U, Gunes Y, Ozcengiz D. Comparison of morphine and tramadol by patient-controlled analgesia for postoperative analgesia after tonsillectomy in children. Paediatric anaesthesia 2005;15:979-84.

46. Karl HW, Tyler DC, Miser AW. Controlled trial of morphine vs hydromorphone for patient-controlled analgesia in children with postoperative pain. Pain Med 2012;13:1658-9.
47. DiGiusto M, Bhalla T, Martin D, Foerschler D, Jones MJ, Tobias JD. Patient-controlled analgesia in the pediatric population: morphine versus hydromorphone. Journal of pain research 2014;7:471-5.
48. Nelson KL, Yaster M, Kost-Byerly S, Monitto CL. A national survey of American Pediatric Anesthesiologists: patient-controlled analgesia and other intravenous opioid therapies in pediatric acute pain management. Anesthesia and analgesia 2010;110:754-60.
49. Doyle E, Harper I, Morton NS. Patient-controlled analgesia with low dose background infusions after lower abdominal surgery in children. British journal of anaesthesia 1993;71:818-22.
50. Doyle E, Robinson D, Morton NS. Comparison of patient-controlled analgesia with and without a background infusion after lower abdominal surgery in children. British journal of anaesthesia 1993;71:670-3.
51. Weldon BC, Connor M, White PF. Pediatric PCA: the role of concurrent opioid infusions and nurse-controlled analgesia. Clin J Pain 1993;9:26-33.
52. McNeely JK, Trentadue NC. Comparison of patient-controlled analgesia with and without nighttime morphine infusion following lower extremity surgery in children. J Pain Symptom Manage 1997;13:268-73.
53. Yildiz K, Tercan E, Dogru K, Ozkan U, Boyaci A. Comparison of patient-controlled analgesia with and without a background infusion after appendicectomy in children. Paediatric anaesthesia 2003;13:427-31.
54. Kelly JJ, Donath S, Jamsen K, Chalkiadis GA. Postoperative sleep disturbance in pediatric patients using patient-controlled devices (PCA). Paediatric anaesthesia 2006;16:1051-6.
55. George JA, Lin EE, Hanna MN, et al. The effect of intravenous opioid patient-controlled analgesia with and without background infusion on respiratory depression: a meta-analysis. J Opioid Manag 2010;6:47-54.
56. Hayes J, Dowling JJ, Peliowski A, Crawford MW, Johnston B. Patient-Controlled Analgesia Plus Background Opioid Infusion for Postoperative Pain in Children: A Systematic Review and Meta-Analysis of Randomized Trials. Anesthesia and analgesia 2016;123:991-1003.
57. Voepel-Lewis T, Marinkovic A, Kostrzewa A, Tait AR, Malviya S. The prevalence of and risk factors for adverse events in children receiving patient-controlled analgesia by proxy or patient-controlled analgesia after surgery. Anesthesia and analgesia 2008;107:70-5.
58. Monitto CL, Greenberg RS, Kost-Byerly S, et al. The safety and efficacy of parent-/nurse-controlled analgesia in patients less than six years of age. Anesthesia and analgesia 2000;91:573-9.
59. Howard RF, Lloyd-Thomas A, Thomas M, et al. Nurse-controlled analgesia (NCA) following major surgery in 10,000 patients in a children's hospital. Paediatric anaesthesia 2010;20:126-34.

60. Choi SH, Lee WK, Lee SJ, et al. Parent-controlled analgesia in children undergoing cleft palate repair. J Korean Med Sci 2008;23:122-5.
61. Czarnecki ML, Salamon KS, Jastrowski Mano KE, Ferrise AS, Sharp M, Weisman SJ. A preliminary report of parent/nurse-controlled analgesia (PNCA) in infants and preschoolers. Clin J Pain 2011;27:102-7.
62. Czarnecki ML, Hainsworth K, Simpson PM, et al. Is there an alternative to continuous opioid infusion for neonatal pain control? A preliminary report of parent/nurse-controlled analgesia in the neonatal intensive care unit. Paediatric anaesthesia 2014;24:377-85.
63. Patient controlled analgesia by proxy. Sentinel event alert / Joint Commission on Accreditation of Healthcare Organizations 2004:1-2.
64. Pasero C, McCaffery M. Authorized and unauthorized use of PCA pumps: clarifying the use of patient-controlled analgesia, in light of recent alerts. Am J Nurs 2005;105:30-1, 3.
65. Kenagy A, Turner H. Pediatric patient-controlled analgesia by proxy. AACN Adv Crit Care 2007;18:361-5.
66. Krane EJ. Patient-controlled analgesia: proxy-controlled analgesia? Anesthesia and analgesia 2008;107:15-7.
67. Naguib AN, Dewhirst E, Winch PD, Simsic J, Galantowicz M, Tobias JD. Pain management after comprehensive stage 2 repair for hypoplastic left heart syndrome. Pediatr Cardiol 2013;34:52-8.
68. Sutters KA, Shaw BA, Gerardi JA, Hebert D. Comparison of morphine patient-controlled analgesia with and without ketorolac for postoperative analgesia in pediatric orthopedic surgery. Am J Orthop (Belle Mead NJ) 1999;28:351-8.
69. Vetter TR, Heiner EJ. Intravenous ketorolac as an adjuvant to pediatric patient-controlled analgesia with morphine. J Clin Anesth 1994;6:110-3.
70. Moreno M, Castejon FJ, Palacio MA. Patient-controlled analgesia with ketorolac in pediatric surgery. J Physiol Biochem 2000;56:209-16.
71. Carney DE, Nicolette LA, Ratner MH, Minerd A, Baesl TJ. Ketorolac reduces postoperative narcotic requirements. J Pediatr Surg 2001;36:76-9.
72. Munro HM, Walton SR, Malviya S, et al. Low-dose ketorolac improves analgesia and reduces morphine requirements following posterior spinal fusion in adolescents. Can J Anaesth 2002;49:461-6.
73. Morton NS, O'Brien K. Analgesic efficacy of paracetamol and diclofenac in children receiving PCA morphine. British journal of anaesthesia 1999;82:715-7.
74. Hong JY, Kim WO, Koo BN, Cho JS, Suk EH, Kil HK. Fentanyl-sparing effect of acetaminophen as a mixture of fentanyl in intravenous parent-/nurse-controlled analgesia after pediatric ureteroneocystostomy. Anesthesiology 2010;113:672-7.
75. Hiller A, Helenius I, Nurmi E, et al. Acetaminophen improves analgesia but does not reduce opioid requirement after major spine surgery in children and adolescents. Spine (Phila Pa 1976) 2012;37:E1225-31.
76. Shum S, Lim J, Page T, et al. An audit of pain management following pediatric day surgery at British Columbia Children's Hospital. Pain Res Manag 2012;17:328-34.

77. Vincent C, Chiappetta M, Beach A, et al. Parents' management of children's pain at home after surgery. J Spec Pediatr Nurs 2012;17:108-20.
78. Fortier MA, Kain ZN. Pain after pediatric surgery. Pain 2015;156:2111-2.
79. Fortier MA, MacLaren JE, Martin SR, Perret-Karimi D, Kain ZN. Pediatric pain after ambulatory surgery: where's the medication? Pediatrics 2009;124:e588-95.
80. Voepel-Lewis T, Zikmund-Fisher BJ, Smith EL, Redman RW, Zyzanski S, Tait AR. Parents' Analgesic Trade-Off Dilemmas: How Analgesic Knowledge Influences Their Decisions to Give Opioids. Clin J Pain 2016;32:187-95.
81. Prows CA, Zhang X, Huth MM, et al. Codeine-related adverse drug reactions in children following tonsillectomy: a prospective study. Laryngoscope 2014;124:1242-50.
82. Yellon RF, Kenna MA, Cladis FP, McGhee W, Davis PJ. What is the best non-codeine postadenotonsillectomy pain management for children? Laryngoscope 2014;124:1737-8.
83. Tobias JD, Green TP, Cote CJ, Section On A, Pain M, Committee On D. Codeine: Time To Say "No". Pediatrics 2016.
84. Smith HS. Opioid metabolism. Mayo Clin Proc 2009;84:613-24.
85. Halling J, Weihe P, Brosen K. CYP2D6 polymorphism in relation to tramadol metabolism: a study of faroese patients. Ther Drug Monit 2008;30:271-5.
86. Cote CJ, Posner KL, Domino KB. Death or neurologic injury after tonsillectomy in children with a focus on obstructive sleep apnea: houston, we have a problem! Anesthesia and analgesia 2014;118:1276-83.
87. Brown KA, Laferriere A, Moss IR. Recurrent hypoxemia in young children with obstructive sleep apnea is associated with reduced opioid requirement for analgesia. Anesthesiology 2004;100:806-10; discussion 5A.
88. Sutters KA, Miaskowski C, Holdridge-Zeuner D, et al. A randomized clinical trial of the efficacy of scheduled dosing of acetaminophen and hydrocodone for the management of postoperative pain in children after tonsillectomy. Clin J Pain 2010;26:95-103.
89. Erskine a, Wiffen PJ, Conlon JA. Postoperative pain relief for children. Cochrane Database Syst Rev 2015;As required versus fixed schedule analgesic administration for postoperative pain in children.
90. Sadhasivam S, Myer CM, 3rd. Preventing opioid-related deaths in children undergoing surgery. Pain Med 2012;13:982-3; author reply 4.
91. Hwang CS, Kang EM, Kornegay CJ, Staffa JA, Jones CM, McAninch JK. Trends in the Concomitant Prescribing of Opioids and Benzodiazepines, 2002-2014. Am J Prev Med 2016;51:151-60.
92. Jones CM, McAninch JK. Emergency Department Visits and Overdose Deaths From Combined Use of Opioids and Benzodiazepines. Am J Prev Med 2015;49:493-501.
93. El-Fattah AM, Ramzy E. Pre-emptive triple analgesia protocol for tonsillectomy pain control in children: double-blind, randomised, controlled, clinical trial. J Laryngol Otol 2013;127:383-91.

94. Mitchell A, van Zanten SV, Inglis K, Porter G. A randomized controlled trial comparing acetaminophen plus ibuprofen versus acetaminophen plus codeine plus caffeine after outpatient general surgery. J Am Coll Surg 2008;206:472-9.
95. Khetani JD, Madadi P, Sommer DD, et al. Apnea and oxygen desaturations in children treated with opioids after adenotonsillectomy for obstructive sleep apnea syndrome: a prospective pilot study. Paediatr Drugs 2012;14:411-5.
96. George JA, Park PS, Hunsberger J, et al. An Analysis of 34,218 Pediatric Outpatient Controlled Substance Prescriptions. Anesthesia and analgesia 2016;122:807-13.
97. Mitra S, Sinatra RS. Perioperative management of acute pain in the opioid-dependent patient. Anesthesiology 2004;101:212-27.
98. Fanning JJ, Stucke AG, Christensen MA, Cassidy LD, Berens RJ. Perioperative opiate requirements in children with previous opiate infusion. Paediatric anaesthesia 2012;22:203-8.
99. Brummett CM, Janda AM, Schueller CM, et al. Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: a prospective, observational cohort study. Anesthesiology 2013;119:1434-43.
100. Brummett CM, Urquhart AG, Hassett AL, et al. Characteristics of fibromyalgia independently predict poorer long-term analgesic outcomes following total knee and hip arthroplasty. Arthritis Rheumatol 2015;67:1386-94.
101. Christo PJ, Manchikanti L, Ruan X, et al. Urine drug testing in chronic pain. Pain Physician 2011;14:123-43.
102. Katz NP, Sherburne S, Beach M, et al. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesthesia and analgesia 2003;97:1097-102, table of contents.
103. Elkassabany N, Speck RM, Oslin D, et al. Preoperative screening and case cancellation in cocaine-abusing veterans scheduled for elective surgery. Anesthesiol Res Pract 2013;2013:149892.
104. Miech RA, Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Secondary school students. Ann Arbor: Institute for Social Research, The University of Michigan. Monitoring the Future national survey results on drug use, 1975-2014 2014;1:599.
105. McCabe SE, West BT, Cranford JA, et al. Medical misuse of controlled medications among adolescents. Arch Pediatr Adolesc Med 2011;165:729-35.
106. McCabe SE, Cranford JA, Boyd CJ, Teter CJ. Motives, diversion and routes of administration associated with nonmedical use of prescription opioids. Addict Behav 2007;32:562-75.
107. The CBHSQ Report: A Day in the Life of American Adolescents: Substance Use Facts Update. Rockville, MD. Sustance Abuse and Mental health Services Administration, Center for Behavioral Health Statistics and Quality 2013.
108. Wasan AD, Correll DJ, Kissin I, O'Shea S, Jamison RN. Iatrogenic addiction in patients treated for acute or subacute pain: a systematic review. J Opioid Manag 2006;2:16-22.

109. Substance Abuse and Mental Health Services Administration, Rusults from the 2013 National Survey on Drug Use and Health: Summary of National Findings. NSDUH Series H-48, HHS Publication No (SMA) 14--4863 2013.
110. McCabe SE, West BT, Boyd CJ. Leftover prescription opioids and nonmedical use among high school seniors: a multi-cohort national study. J Adolesc Health 2013;52:480-5.
111. Ross-Durow PL, McCabe SE, Boyd CJ. Adolescents' Access to their own prescription medications in the home. . Journal of Adolescent Health 2013;53:260-4.
112. McCabe SE, West BT, Teter CJ, Cranford JA, Ross-Durow PL, Boyd CJ. Adolescent nonmedical users of prescription opioids: brief screening and substance use disorders. Addict Behav 2012;37:651-6.
113. Mitchell SG, Kelly SM, Gryczynski J, et al. The CRAFFT cut-points and DSM-5 criteria for alcohol and other drugs: a reevaluation and reexamination. Subst Abus 2014;35:376-80.
114. Roberts DM, Meyer-Witting M. High-dose buprenorphine: perioperative precautions and management strategies. Anaesth Intensive Care 2005;33:17-25.
115. Health AAoPCoPAoCaF, Task Force on Pain in Infants C, and Adolescents. The assessment and management of acute pain in infants, children, and adolescents. Pediatrics 2001;108:793-7.
116. Ireland AoPAoGBa. Good practice in postoperative and procedural pain management, 2nd edition. Paediatr Anaesth 2012;22 Suppl 1:1-79.
117. Cohen LL, Lemanek K, Blount RL, et al. Evidence-based assessment of pediatric pain. J Pediatr Psychol 2008;33:939-55; discussion 56-7.
118. Stapelkamp C, Carter B, Gordon J, Watts C. Assessment of acute pain in children: development of evidence-based guidelines. Int J Evid Based Healthc 2011;9:39-50.
119. Kozlowski LJ, Kost-Byerly S, Colantuoni E, et al. Pain prevalence, intensity, assessment and management in a hospitalized pediatric population. Pain Manag Nurs 2014;15:22-35.
120. Franck LS, Bruce E. Putting pain assessment into practice: why is it so painful? Pain Res Manag 2009;14:13-20.
121. Stevens BJ, Harrison D, Rashotte J, et al. Pain assessment and intensity in hospitalized children in Canada. J Pain 2012;13:857-65.
122. Zisk-Rony RY, Lev J, Haviv H. Nurses' report of in-hospital pediatric pain assessment: examining challenges and perspectives. Pain Manag Nurs 2015;16:112-20.
123. Taylor EM, Boyer K, Campbell FA. Pain in hospitalized children: a prospective cross-sectional survey of pain prevalence, intensity, assessment and management in a Canadian pediatric teaching hospital. Pain Res Manag 2008;13:25-32.
124. Schiavenato M, Craig KD. Pain assessment as a social transaction: beyond the "gold standard". Clin J Pain 2010;26:667-76.
125. van Dijk JF, van Wijck AJ, Kappen TH, Peelen LM, Kalkman CJ, Schuurmans MJ. Postoperative pain assessment based on numeric ratings is not the same for patients and professionals: a cross-sectional study. Int J Nurs Stud 2012;49:65-71.

126. von Baeyer CL. Children's self-report of pain intensity: what we know, where we are headed. Pain Res Manag 2009;14:39-45.
127. Twycross A, Voepel-Lewis T, Vincent C, Franck LS, von Baeyer CL. A debate on the proposition that self-report is the gold standard in assessment of pediatric pain intensity. Clin J Pain 2015;31:707-12.
128. Voepel-Lewis T. How reliable are 'valid and reliable' pain scores in the pediatric clinical setting? Pain Manag 2013;3:343-50.
129. Huguet A, Stinson JN, McGrath PJ. Measurement of self-reported pain intensity in children and adolescents. J Psychosom Res 2010;68:329-36.
130. Tomlinson D, von Baeyer CL, Stinson JN, Sung L. A systematic review of faces scales for the self-report of pain intensity in children. Pediatrics 2010;126:e1168-98.
131. von Baeyer CL, Forsyth SJ, Stanford EA, Watson M, Chambers CT. Response biases in preschool children's ratings of pain in hypothetical situations. Eur J Pain 2009;13:209-13.
132. Vervoort T, Trost Z, Van Ryckeghem DM. Children's selective attention to pain and avoidance behaviour: the role of child and parental catastrophizing about pain. Pain 2013;154:1979-88.
133. Stinson JN, Kavanagh T, Yamada J, Gill N, Stevens B. Systematic review of the psychometric properties, interpretability and feasibility of self-report pain intensity measures for use in clinical trials in children and adolescents. Pain 2006;125:143-57.
134. von Baeyer CL. Numerical rating scale for self-report of pain intensity in children and adolescents: recent progress and further questions. Eur J Pain 2009;13:1005-7.
135. McGrath PJ, Walco GA, Turk DC, et al. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. J Pain 2008;9:771-83.
136. Bernard R, Salvi N, Gall O, et al. MORPHIT: an observational study on morphine titration in the postanesthetic care unit in children. Paediatric anaesthesia 2014;24:303-8.
137. Voepel-Lewis T, Malviya S. Pain score guided morphine titration is risky and inappropriate. Paediatric anaesthesia 2014;24:454-6.
138. Joint Commission Sentinel Event Alert. Safe use of opioids in hospitals. . Sentinel Event Alert 2012;49.
139. Commission J. Safe use of opioids in hospitals. Chicago: Joint Commission; 2012 2012.
140. Crellin D, Sullivan TP, Babl FE, O'Sullivan R, Hutchinson A. Analysis of the validation of existing behavioral pain and distress scales for use in the procedural setting. Paediatric anaesthesia 2007;17:720-33.
141. von Baeyer CL, Spagrud LJ. Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. Pain 2007;127:140-50.
142. Blount RL, Loiselle KA. Behavioural assessment of pediatric pain. Pain Res Manag 2009;14:47-52.

143. Bernard R, Salvi N, Gall O, et al. MORPHIT: an observational study on morphine titration in the postanesthetic care unit in children. Paediatr Anaesth 2013.
144. Kokki H, Lintula H, Vanamo K, Heiskanen M, Eskelinen M. Oxycodone vs placebo in children with undifferentiated abdominal pain: a randomized, double-blind clinical trial of the effect of analgesia on diagnostic accuracy. Arch Pediatr Adolesc Med 2005;159:320-5.
145. Page MG, Stinson J, Campbell F, Isaac L, Katz J. Pain-related psychological correlates of pediatric acute post-surgical pain. J Pain Res 2012;5:547-58.
146. Voepel-Lewis T, Burke CN, Jeffreys N, Malviya S, Tait AR. Do 0-10 numeric rating scores translate into clinically meaningful pain measures for children? Anesthesia and analgesia 2011;112:415-21.
147. Voepel-Lewis T, Merkel S, Tait AR, Trzcinka A, Malviya S. The reliability and validity of the Face, Legs, Activity, Cry, Consolability observational tool as a measure of pain in children with cognitive impairment. Anesthesia and analgesia 2002;95:1224-9, table of contents.
148. Page MG, Katz J, Stinson J, Isaac L, Martin-Pichora AL, Campbell F. Validation of the numerical rating scale for pain intensity and unpleasantness in pediatric acute postoperative pain: sensitivity to change over time. J Pain 2012;13:359-69.
149. Boerlage AA, Ista E, Duivenvoorden HJ, de Wildt SN, Tibboel D, van Dijk M. The COMFORT behaviour scale detects clinically meaningful effects of analgesic and sedative treatment. Eur J Pain 2015;19:473-9.
150. Tsze DS, Hirschfeld G, von Baeyer CL, Bulloch B, Dayan PS. Clinically significant differences in acute pain measured on self-report pain scales in children. Acad Emerg Med 2015;22:415-22.
151. Foster RL, Yucha CB, Zuk J, Vojir CP. Physiologic correlates of comfort in healthy children. Pain Manag Nurs 2003;4:23-30.
152. van Dijk M, de Boer JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. Pain 2000;84:367-77.
153. Gall O, Champigneulle B, Schweitzer B, et al. Postoperative pain assessment in children: a pilot study of the usefulness of the analgesia nociception index. British journal of anaesthesia 2015;115:890-5.
154. Chambers CT, Finley GA, McGrath PJ, Walsh TM. The parents' postoperative pain measure: replication and extension to 2-6-year-old children. Pain 2003;105:437-43.
155. von Baeyer CL, Chambers CT, Eakins DM. Development of a 10-item short form of the parents' postoperative pain measure: the PPPM-SF. J Pain 2011;12:401-6.
156. von Baeyer CL, Lin V, Seidman LC, Tsao JC, Zeltzer LK. Pain charts (body maps or manikins) in assessment of the location of pediatric pain. Pain Manag 2011;1:61-8.
157. Hamill JK, Lyndon M, Liley A, Hill AG. Where it hurts: A systematic review of pain-location tools for children. Pain 2014;155:851-8.

158. Fernandes AM, De Campos C, Batalha L, Perdigao A, Jacob E. Pain assessment using the adolescent pediatric pain tool: a systematic review. Pain Res Manag 2014;19:212-8.
159. American Society of Anesthesiologists Task Force on Acute Pain M. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248-73.
160. Weinger MB. No patient shall be harmed by opioid-induced respiratory depression. APSF Newsletter 2011;26:26-8.
161. Safe use of opioids in hospitals. Sentinel Event Alert 2012:1-5.
162. CMS guidelines. Requirements for Hospital Medication Administration, Particularly Intravenous Medications and Post-operative Care of Patients Receiving IV Opioids.
163. Jarzyna D, Jungquist CR, Pasero C, et al. American Society for Pain Management Nursing guidelines on monitoring for opioid-induced sedation and respiratory depression. Pain Manag Nurs 2011;12:118-45 e10.
164. Cooney MF, Czarnecki M, Dunwoody C, et al. American Society for Pain Management Nursing position statement with clinical practice guidelines: authorized agent controlled analgesia. Pain Manag Nurs 2013;14:176-81.
165. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. The journal of pain : official journal of the American Pain Society 2016;17:131-57.
166. Chidambaran V, Olbrecht V, Hossain M, Sadhasivam S, Rose J, Meyer MJ. Risk predictors of opioid-induced critical respiratory events in children: naloxone use as a quality measure of opioid safety. Pain Med 2014;15:2139-49.
167. Miller KM, Kim AY, Yaster M, et al. Long-term tolerability of capnography and respiratory inductance plethysmography for respiratory monitoring in pediatric patients treated with patient-controlled analgesia. Paediatric anaesthesia 2015;25:1054-9.
168. Morton NS, Errera A. APA national audit of pediatric opioid infusions. Paediatric anaesthesia 2010;20:119-25.
169. Overdyk FJ, Carter R, Maddox RR, Callura J, Herrin AE, Henriquez C. Continuous oximetry/capnometry monitoring reveals frequent desaturation and bradypnea during patient-controlled analgesia. Anesthesia and analgesia 2007;105:412-8.
170. Maddox RR, Williams CK. Clinical Experience with capnography monitoring for PCA patients Anesthesia Patient Safety Foundation. . Anesthesia Patient Safety Newsletter 2012.
171. Voscopoulos CJ, MacNabb CM, Freeman J, Galvagno SM, Jr., Ladd D, George E. Continuous noninvasive respiratory volume monitoring for the identification of patients at risk for opioid-induced respiratory depression and obstructive breathing patterns. J Trauma Acute Care Surg 2014;77:S208-15.

172. Tobias JD. Transcutaneous carbon dioxide monitoring in infants and children. Paediatric anaesthesia 2009;19:434-44.
173. Bernet-Buettiker V, Ugarte MJ, Frey B, Hug MI, Baenziger O, Weiss M. Evaluation of a new combined transcutaneous measurement of PCO2/pulse oximetry oxygen saturation ear sensor in newborn patients. Pediatrics 2005;115:e64-8.
174. Hansen TG, Henneberg SW, Hole P. Age-related postoperative morphine requirements in children following major surgery--an assessment using patient-controlled analgesia (PCA). Eur J Pediatr Surg 1996;6:29-31.
175. Malviya S, Voepel-Lewis T, Tait AR, et al. Pain management in children with and without cognitive impairment following spine fusion surgery. Paediatric anaesthesia 2001;11:453-8.
176. Hudcova J, McNicol E, Quah C, Lau J, Carr DB. Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Cochrane Database Syst Rev 2006:CD003348.
177. Gordon DB, Pellino TA, Higgins GA, Pasero C, Murphy-Ende K. Nurses' opinions on appropriate administration of PRN range opioid analgesic orders for acute pain. Pain Manag Nurs 2008;9:131-40.
178. Pasero C. Assessment of sedation during opioid administration for pain management. J Perianesth Nurs 2009;24:186-90.
179. Lee LA, Caplan RA, Stephens LS, et al. Postoperative opioid-induced respiratory depression: a closed claims analysis. Anesthesiology 2015;122:659-65.
180. Rosenfeld DM, Betcher JA, Shah RA, et al. Findings of a Naloxone Database and its Utilization to Improve Safety and Education in a Tertiary Care Medical Center. Pain Pract 2016;16:327-33.
181. Voepel-Lewis T, Wagner D, Burke C. Early adjuvant use of non-opioids associated with reduced odds of serious postoperative opioid adverse events and need for rescue in children. . Ped Anesth 2013:162-9.
182. Taenzer AH, Pyke JB, McGrath SP. A review of current and emerging approaches to address failure-to-rescue. Anesthesiology 2011;115:421-31.
183. Curry JP, Jungquist CR. A critical assessment of monitoring practices, patient deterioration, and alarm fatigue on inpatient wards: a review. Patient Saf Surg 2014;8:29.
184. Oderda GM, Gan TJ, Johnson BH, Robinson SB. Effect of opioid-related adverse events on outcomes in selected surgical patients. Journal of pain & palliative care pharmacotherapy 2013;27:62-70.
185. Oderda GM, Said Q, Evans RS, et al. Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay. The Annals of pharmacotherapy 2007;41:400-6.
186. Sadhasivam S, Chidambaran V, Goodman H, Plapp R, McAuliffe J. Pharmacogenetics and personalizing perioperative analgesia in children. Journal of Pain 2010;1):S50.
187. Somogyi AA, Coller JK, Barratt DT. Pharmacogenetics of opioid response. Clinical pharmacology and therapeutics 2015;97:125-7.

188. Sadhasivam S, Chidambaran V, Ngamprasertwong P, et al. Race and unequal burden of perioperative pain and opioid related adverse effects in children. Pediatrics 2012;129:832-8.
189. Brown KA, Laferriere A, Lakheeram I, Moss IR. Recurrent hypoxemia in children is associated with increased analgesic sensitivity to opiates. Anesthesiology 2006;105:665-9.
190. Chung F, Liao P, Elsaid H, Shapiro CM, Kang W. Factors associated with postoperative exacerbation of sleep-disordered breathing. Anesthesiology 2014;120:299-311.
191. Ingrande J, Lemmens HJ. Dose adjustment of anaesthetics in the morbidly obese. British journal of anaesthesia 2010;105 Suppl 1:i16-23.
192. Mortensen A, Lenz K, Abildstrom H, Lauritsen TL. Anesthetizing the obese child. Paediatric anaesthesia 2011;21:623-9.
193. Callaghan LC, Walker JD. An aid to drug dosing safety in obese children: development of a new nomogram and comparison with existing methods for estimation of ideal body weight and lean body mass. Anaesthesia 2015;70:176-82.
194. Nakatsuka N, Minogue SC, Lim J, et al. Intravenous nalbuphine 50 microg x kg(-1) is ineffective for opioid-induced pruritus in pediatrics. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2006;53:1103-10.
195. Jannuzzi RG. Nalbuphine for Treatment of Opioid-induced Pruritus: A Systematic Review of Literature. Clin J Pain 2016;32:87-93.
196. West N, Ansermino JM, Carr RR, Leung K, Zhou G, Lauder GR. A naloxone admixture to prevent opioid-induced pruritus in children: a randomized controlled trial. Can J Anaesth 2015;62:891-900.
197. Monitto CL, Kost-Byerly S, White E, et al. The Optimal Dose of Prophylactic Intravenous Naloxone in Ameliorating Opioid-Induced Side Effects in Children Receiving Intravenous Patient-Controlled Analgesia Morphine for Moderate to Severe Pain: A Dose Finding Study. Anesthesia and Analgesia 2011;113:834-42.
198. Maxwell LG, Kaufmann SC, Bitzer S, et al. The effects of a small-dose naloxone infusion on opioid-induced side effects and analgesia in children and adolescents treated with intravenous patient-controlled analgesia: a double-blind, prospective, randomized, controlled study. Anesthesia and analgesia 2005;100:953-8.
199. Wennstrom B, Reinsfelt B. Rectally administered diclofenac (Voltaren) reduces vomiting compared with opioid (morphine) after strabismus surgery in children. Acta Anaesthesiologica Scandinavica 2002;46:430-4.
200. Moiniche S, Romsing J, Dahl JB, Tramer MR. Nonsteroidal antiinflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. Anesthesia & Analgesia 2003;96:68-77, table of contents.
201. Munro HM, Riegger LQ, Reynolds PI, Wilton NC, Lewis IH. Comparison of the analgesic and emetic properties of ketorolac and morphine for paediatric outpatient strabismus surgery. British journal of anaesthesia 1994;72:624-8.
202. Mather SJ, Peutrell JM. Postoperative morphine requirements, nausea and vomiting following anaesthesia for tonsillectomy. Comparison of intravenous morphine and non-opioid analgesic techniques. Paediatric anaesthesia 1995;5:185-8.

203. Heyland K, Dangel P, Gerber AC. Postoperative nausea and vomiting (PONV) in children. European Journal of Pediatric Surgery 1997;7:230-3.
204. Kokki H, Homan E, Tuovinen K, Purhonen S. Peroperative treatment with i.v. ketoprofen reduces pain and vomiting in children after strabismus surgery. Acta Anaesthesiologica Scandinavica 1999;43:13-8.
205. Keidan I, Zaslansky R, Eviatar E, Segal S, Sarfaty SM. Intraoperative ketorolac is an effective substitute for fentanyl in children undergoing outpatient adenotonsillectomy. Paediatric anaesthesia 2004;14:318-23.
206. Sneyd JR, Carr A, Byrom WD, Bilski AJ. A meta-analysis of nausea and vomiting following maintenance of anaesthesia with propofol or inhalational agents. European Journal of Anaesthesiology 1998;15:433-45.
207. Padda GS, Cruz OA, Krock JL. Comparison of postoperative emesis, recovery profile, and analgesia in pediatric strabismus repair. Rectal acetaminophen versus intravenous fentanyl-droperidol. Ophthalmology 1997;104:419-24.
208. Jensen AB, Christiansen DB, Coulthard K, et al. Tropisetron reduces postoperative vomiting in children undergoing tonsillectomy. Paediatric anaesthesia 2000;10:69-75.
209. Nolan J, Prosser DP. Prevention of postoperative vomiting with granisetron in paediatric patients with and without a history of motion sickness. Paediatric anaesthesia 2000;10:451-2.
210. Smith PV, Walton DS. Prevention of vomiting after general anesthesia for pediatric ophthalmic surgery. AANA Journal 2001;69:39-43.
211. De Negri P, Ivani G. Management of postoperative nausea and vomiting in children. Pediatric Drugs 2002;4:717-28.
212. Anderson BJ, Ralph CJ, Stewart AW, Barber C, Holford NH. The dose-effect relationship for morphine and vomiting after day-stay tonsillectomy in children. Anaesthesia & Intensive Care 2000;28:155-60.
213. Eberhart LH, Geldner G, Kranke P, et al. The development and validation of a risk score to predict the probability of postoperative vomiting in pediatric patients. Anesthesia & Analgesia 2004;99:1630-7, table of contents.
214. Duedahl TH, Hansen EH. A qualitative systematic review of morphine treatment in children with postoperative pain. Paediatr Anaesth 2007;17:756-74.
215. Monitto CL, Kost-Byerly S, White E, et al. The optimal dose of prophylactic intravenous naloxone in ameliorating opioid-induced side effects in children receiving intravenous patient-controlled analgesia morphine for moderate to severe pain: a dose finding study. Anesthesia and analgesia 2011;113:834-42.
216. Doyle E, Byers G, McNicol LR, Morton NS. Prevention of postoperative nausea and vomiting with transdermal hyoscine in children using patient-controlled analgesia. British journal of anaesthesia 1994;72:72-6.
217. Allen D, Jorgensen C, Sims C. Effect of tropisetron on vomiting during patient-controlled analgesia in children. British journal of anaesthesia 1999;83:608-10.
218. Park YH, Jang YE, Byon HJ, Kim JT, Kim HS. Comparison of the efficacy of ramosetron and ondansetron in the prophylaxis of postoperative vomiting in children receiving fentanyl by patient-controlled analgesia after orthopedic surgery: a randomized controlled trial. Paediatric anaesthesia 2013;23:360-4.

219. Kokinsky E, Thornberg E, Nilsson K, Larsson LE. Postoperative nausea and vomiting in children using patient-controlled analgesia: the effect of prophylactic intravenous dixyrazine. Acta Anaesthesiol Scand 1999;43:191-5.
220. Nakatsuka N, Minogue SC, Lim J, et al. Intravenous nalbuphine 50 microg x kg(-1) is ineffective for opioid-induced pruritus in pediatrics. Can J Anaesth 2006;53:1103-10.
221. Prakash S, Mehra V, Gogia AR. Fentanyl induced rigidity in an infant. J Anaesthesiol Clin Pharmacol 2010;26:567-8.
222. Fahnenstich H, Steffan J, Kau N, Bartmann P. Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. Crit Care Med 2000;28:836-9.
223. Bennett JA, Abrams JT, Van Riper DF, Horrow JC. Difficult or impossible ventilation after sufentanil-induced anesthesia is caused primarily by vocal cord closure. Anesthesiology 1997;87:1070-4.
224. Carvalho B, Mirikitani EJ, Lyell D, Evans DA, Druzin M, Riley ET. Neonatal chest wall rigidity following the use of remifentanil for cesarean delivery in a patient with autoimmune hepatitis and thrombocytopenia. Int J Obstet Anesth 2004;13:53-6.
225. Lindemann R. Respiratory muscle rigidity in a preterm infant after use of fentanyl during Caesarean section. Eur J Pediatr 1998;157:1012-3.
226. Dewhirst E, Naguib A, Tobias JD. Chest wall rigidity in two infants after low-dose fentanyl administration. Pediatr Emerg Care 2012;28:465-8.
227. Choong K, AlFaleh K, Doucette J, et al. Remifentanil for endotracheal intubation in neonates: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2010;95:F80-4.
228. Peters JW, Schouw R, Anand KJ, van Dijk M, Duivenvoorden HJ, Tibboel D. Does neonatal surgery lead to increased pain sensitivity in later childhood? Pain 2005;114:444-54.
229. de Graaf J, van den Akker EL, van Lingen RA, et al. Five-year follow-up of effects of neonatal intensive care and morphine infusion during mechanical ventilation on diurnal cortisol rhythm. J Pediatr 2014;165:459-63 e2.
230. Vinall J, Miller SP, Chau V, Brummelte S, Synnes AR, Grunau RE. Neonatal pain in relation to postnatal growth in infants born very preterm. Pain 2012;153:1374-81.
231. Lammers EM, Johnson PN, Ernst KD, et al. Association of fentanyl with neurodevelopmental outcomes in very-low-birth-weight infants. Ann Pharmacother 2014;48:335-42.
232. Ranger M, Synnes AR, Vinall J, Grunau RE. Internalizing behaviours in school-age children born very preterm are predicted by neonatal pain and morphine exposure. Eur J Pain 2014;18:844-52.
233. Anand KJ, Hickey PR. Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. New England Journal of Medicine 1992;326:1-9.

234. Crawford MW, Hickey C, Zaarour C, Howard A, Naser B. Development of acute opioid tolerance during infusion of remifentanil for pediatric scoliosis surgery. Anesthesia and analgesia 2006;102:1662-7.
235. Stricker PA, Kraemer FW, Ganesh A. Severe remifentanil-induced acute opioid tolerance following awake craniotomy in an adolescent. J Clin Anesth 2009;21:124-6.
236. Kim SH, Lee MH, Seo H, Lee IG, Hong JY, Hwang JH. Intraoperative infusion of 0.6-0.9 micro gkg(-1)min(-1) remifentanil induces acute tolerance in young children after laparoscopic ureteroneocystostomy. Anesthesiology 2013;118:337-43.
237. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. British journal of anaesthesia 2014;112:991-1004.
238. Kim SH, Stoicea N, Soghomonyan S, Bergese SD. Remifentanil-acute opioid tolerance and opioid-induced hyperalgesia: a systematic review. Am J Ther 2015;22:e62-74.
239. Hood DD, Curry R, Eisenach JC. Intravenous remifentanil produces withdrawal hyperalgesia in volunteers with capsaicin-induced hyperalgesia. Anesthesia and analgesia 2003;97:810-5.
240. Roulleau P, Gall O, Desjeux L, Dagher C, Murat I. Remifentanil infusion for cleft palate surgery in young infants. Paediatric anaesthesia 2003;13:701-7.
241. Hallett BR, Chalkiadis GA. Suspected opioid-induced hyperalgesia in an infant. British journal of anaesthesia 2012;108:116-8.
242. Welzing L, Link F, Junghaenel S, et al. Remifentanil-induced tolerance, withdrawal or hyperalgesia in infants: A randomized controlled trial. RAPIP trial: Remifentanil-based analgesia and sedation of paediatric intensive care patients. Neonatology 2013;104:34-41.
243. Engelhardt T, Zaarour C, Naser B, et al. Intraoperative low-dose ketamine does not prevent a remifentanil-induced increase in morphine requirement after pediatric scoliosis surgery. Anesthesia and analgesia 2008;107:1170-5.
244. McDonnell C, Zaarour C, Hull R, et al. Pre-treatment with morphine does not prevent the development of remifentanil-induced hyperalgesia. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2008;55:813-8.
245. Wong I, St John-Green C, Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children. Paediatr Anaesth 2013;23:475-95.
246. Michelet D, Andreu-Gallien J, Bensalah T, et al. A meta-analysis of the use of nonsteroidal antiinflammatory drugs for pediatric postoperative pain. Anesthesia & Analgesia 2012;114:393-406.
247. van der Marel CD, Peters JW, Bouwmeester NJ, Jacqz-Aigrain E, van den Anker JN, Tibboel D. Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants. Br J Anaesth 2007;98:372-9.
248. Morton NS, O'Brien K. Analgesic efficacy of paracetamol and diclofenac in children receiving PCA morphine. Br J Anaesth 1999;82:715-7.
249. Birmingham PK, Tobin MJ, Fisher DM, Henthorn TK, Hall SC, Cote CJ. Initial and subsequent dosing of rectal acetaminophen in children: a 24-hour

pharmacokinetic study of new dose recommendations. Anesthesiology 2001;94:385-9.
250. Apfel CC, Turan A, Souza K, Pergolizzi J, Hornuss C. Intravenous acetaminophen reduces postoperative nausea and vomiting: a systematic review and meta-analysis. Pain 2013;154:677-89.
251. Kossowsky J, Donado C, Berde CB. Immediate rescue designs in pediatric analgesic trials: a systematic review and meta-analysis. Anesthesiology 2015;122:150-71.
252. Dix P, Martindale S, Stoddart PA. Double-blind randomized placebo-controlled trial of the effect of ketamine on postoperative morphine consumption in children following appendicectomy. Paediatric anaesthesia 2003;13:422-6.
253. Becke K, Albrecht S, Schmitz B, et al. Intraoperative low-dose S-ketamine has no preventive effects on postoperative pain and morphine consumption after major urological surgery in children. Paediatric anaesthesia 2005;15:484-90.
254. Jabbour HJ, Naccache NM, Jawish RJ, et al. Ketamine and magnesium association reduces morphine consumption after scoliosis surgery: prospective randomised double-blind study. Acta Anaesthesiol Scand 2014;58:572-9.
255. Cha MH, Eom JH, Lee YS, et al. Beneficial effects of adding ketamine to intravenous patient-controlled analgesia with fentanyl after the Nuss procedure in pediatric patients. Yonsei Med J 2012;53:427-32.
256. Min TJ, Kim WY, Jeong WJ, et al. Effect of ketamine on intravenous patient-controlled analgesia using hydromorphone and ketorolac after the Nuss surgery in pediatric patients. Korean journal of anesthesiology 2012;62:142-7.
257. Pestieau SR, Finkel JC, Junqueira MM, et al. Prolonged perioperative infusion of low-dose ketamine does not alter opioid use after pediatric scoliosis surgery. Paediatric anaesthesia 2014;24:582-90.
258. Perello M, Artes D, Pascuets C, Esteban E, Ey AM. Prolonged Perioperative Low-Dose Ketamine Does Not Improve Short and Long-term Outcomes After Pediatric Idiopathic Scoliosis Surgery. Spine (Phila Pa 1976) 2016.
259. Dahmani S, Delivet H, Hilly J. Emergence delirium in children: an update. Curr Opin Anaesthesiol 2014;27:309-15.
260. Cho HK, Kim KW, Jeong YM, Lee HS, Lee YJ, Hwang SH. Efficacy of ketamine in improving pain after tonsillectomy in children: meta-analysis. PLoS ONE 2014;9:e101259.
261. Jouguelet-Lacoste J, La Colla L, Schilling D, Chelly JE. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Pain Med 2015;16:383-403.
262. Wang L, Johnston B, Kaushal A, Cheng D, Zhu F, Martin J. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials. Can J Anaesth 2016;63:311-25.
263. Sadhasivam S, Boat A, Mahmoud M. Comparison of patient-controlled analgesia with and without dexmedetomidine following spine surgery in children. J Clin Anesth 2009;21:493-501.

264. Jones JS, Cotugno RE, Singhal NR, et al. Evaluation of dexmedetomidine and postoperative pain management in patients with adolescent idiopathic scoliosis: conclusions based on a retrospective study at a tertiary pediatric hospital. Pediatr Crit Care Med 2014;15:e247-52.
265. Rusy LM, Hainsworth KR, Nelson TJ, et al. Gabapentin use in pediatric spinal fusion patients: a randomized, double-blind, controlled trial. Anesthesia and analgesia 2010;110:1393-8.
266. Mayell A, Srinivasan I, Campbell F, Peliowski A. Analgesic effects of gabapentin after scoliosis surgery in children: a randomized controlled trial. Paediatric anaesthesia 2014;24:1239-44.
267. Kranke P, Jokinen J, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Database Syst Rev 2015;7:CD009642.
268. Vigneault L, Turgeon AF, Cote D, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. Can J Anaesth 2011;58:22-37.
269. Sun Y, Li T, Wang N, Yun Y, Gan TJ. Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. Dis Colon Rectum 2012;55:1183-94.
270. McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. Drugs 2010;70:1149-63.
271. Barreveld A, Witte J, Chahal H, Durieux ME, Strichartz G. Preventive analgesia by local anesthetics: the reduction of postoperative pain by peripheral nerve blocks and intravenous drugs. Anesth Analg 2013;116:1141-61.
272. Shen YD, Chen CY, Wu CH, Cherng YG, Tam KW. Dexamethasone, ondansetron, and their combination and postoperative nausea and vomiting in children undergoing strabismus surgery: a meta-analysis of randomized controlled trials. Paediatr Anaesth 2014;24:490-8.
273. Sinha R, Shende D, Maitra S, Kumar N, Ray BR, Mohan VK. Granisetron versus Granisetron-Dexamethasone for Prevention of Postoperative Nausea and Vomiting in Pediatric Strabismus Surgery: A Randomized Double-Blind Trial. Anesthesiology Research and Practice 2016;2016:4281719.
274. Steward DL, Grisel J, Meinzen-Derr J. Steroids for improving recovery following tonsillectomy in children. Cochrane Database Syst Rev 2011:CD003997.
275. Aouad MT, Nasr VG, Yazbeck-Karam VG, et al. A comparison between dexamethasone and methylprednisolone for vomiting prophylaxis after tonsillectomy in inpatient children: A randomized trial. Anesthesia and Analgesia 2012;115:913-20.
276. De Oliveira GS, Jr., Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology 2011;115:575-88.
277. De Oliveira GS, Jr., Castro-Alves LJ, Ahmad S, Kendall MC, McCarthy RJ. Dexamethasone to prevent postoperative nausea and vomiting: an updated meta-analysis of randomized controlled trials. Anesth Analg 2013;116:58-74.

278. Kim MS, Cote CJ, Cristoloveanu C, et al. There is no dose-escalation response to dexamethasone (0.0625-1.0 mg/kg) in pediatric tonsillectomy or adenotonsillectomy patients for preventing vomiting, reducing pain, shortening time to first liquid intake, or the incidence of voice change. Anesthesia and analgesia 2007;104:1052-8, tables of contents.
279. Jimenez N, Anderson GD, Shen DD, et al. Is ethnicity associated with morphine's side effects in children? Morphine pharmacokinetics, analgesic response, and side effects in children having tonsillectomy. Paediatric anaesthesia 2012;22:669-75.
280. Sadhasivam S, Chidambaran V, Olbrecht VA, et al. Opioid-related adverse effects in children undergoing surgery: unequal burden on younger girls with higher doses of opioids. Pain Medicine 2015;16:985-97.
281. Ilfeld BM, Morey TE, Wang RD, Enneking FK. Continuous popliteal sciatic nerve block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. Anesthesiology 2002;97:959-65.
282. Ilfeld BM, Morey TE, Enneking FK. Continuous infraclavicular brachial plexus block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. Anesthesiology 2002;96:1297-304.
283. Ivani G, Mossetti V. Continuous central and perineural infusions for postoperative pain control in children. Curr Opin Anaesthesiol 2010;23:637-42.
284. Richman JM, Liu SS, Courpas G, et al. Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. Anesthesia and analgesia 2006;102:248-57.
285. Bai SJ, Koo BN, Kim JH, Doh PS, Kim KH, Shin YS. Comparison of continuous epidural and intravenous analgesia for postoperative pain control in pediatric lower extremity surgery. Yonsei Med J 2004;45:789-95.
286. Suresh S, Barcelona SL, Young NM, Heffner CL, Cote CJ. Does a preemptive block of the great auricular nerve improve postoperative analgesia in children undergoing tympanomastoid surgery? Anesthesia and analgesia 2004;98:330-3, table of contents.